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TITLE: Interrelationships of Prenatal and Postnatal Growth, Hormones, Diet, and Breast Cancer

PRINCIPAL INVESTIGATOR: Maureen Sanderson, Ph.D.

CONTRACTING ORGANIZATION: The University of Texas Health Science Center
Houston, TX 77225-0036

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14. ABSTRACT

The purpose of this Career Development Award was to expand Dr. Sanderson's current breast cancer research from the effect of intrauterine exposure to estrogen on breast cancer to the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Based on these interrelationships, we hypothesized that insulin resistance would be positively associated with breast cancer, and that genetic susceptibility, and adolescent/adult diet and physical activity would modify the effect of insulin resistance on breast cancer. Specific aims were: 1) to undergo intensive training in cancer biology, and nutritional, molecular and genetic epidemiology, 2) to obtain funding to conduct casecontrol studies of the insulin resistance-breast cancer relationship, and 3) to obtain funding to conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels. During the study, Dr. Sanderson co-taught or audited courses in cancer biology, and nutritional, molecular and genetic epidemiology; received funding as Principal Investigator of the research institution of a HBCU/MI Partnership Award from the Department of Defense to conduct a case-control study of insulin resistance and breast cancer; and submitted a grant to the National Cancer Institute to follow a cohort of children of gestational diabetics from birth through age 12 years to investigate hormone levels in cord blood and subsequent childhood weight, height, diet and physical activity.

15. SUBJECT TERMS
Epidemiology/biostatistics, nutrition, hormone metabolism

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Introduction

The purpose of this Career Development Award was to expand Dr. Sanderson's current breast cancer research from the effect of intrauterine exposure to estrogen on breast cancer to the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. Based on these interrelationships, we hypothesized that insulin resistance would be positively associated with breast cancer. Further, we hypothesized that genetic susceptibility, and adolescent/adult diet and physical activity would modify the effect of insulin resistance on breast cancer. Specific aims were: 1) to undergo intensive training in cancer biology, and nutritional, molecular and genetic epidemiology, 2) to obtain funding to conduct case-control studies of the insulin resistance-breast cancer relationship, and 3) to obtain funding to conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels.

Body

The transfer of this Career Development Award from the University of South Carolina to the University of Texas-Houston School of Public Health at Brownsville was effective August 25, 2003. Due to the two year transfer period the new performance period of the award is May 8, 2000 – March 31, 2006. At the suggestion of my first annual report review, I sent a revised Statement of Work on August 21, 2001 (Appendix A). As a result of my relocation some of the tasks that were planned for months 1-24 will be completed during months 25-48.

During the first year of the study, I completed Task 1.a. by auditing Pathology of Neoplasia with Dr. Kim Creek at the University of South Carolina School of Medicine in Fall 2000 (Appendix B). I partially completed Task 1.c. by authoring the manuscript "Abortion history and breast cancer: results from the Shanghai Breast Cancer Study" (Appendix C). I partially completed Task 1.e. by submitting an Idea Award to the Department of Defense (DOD) entitled "Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer" in June 2000 (Appendix D contains the abstract).

During the second year of the study, I partially completed Task 1.c. by authoring the manuscript "Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population" (Appendix E) and by co-authoring the manuscript "Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India" (Appendix F). I partially completed Task 1.e. by submitting a preproposal for a HBCU/MI Partnership Award to the DOD to investigate insulin resistance and breast cancer with investigators from the University of Texas at Brownsville (UTB, Dr. Gerson Peltz, PI) and from the University of Texas School of Public Health (UTSPH, Dr. Maureen Sanderson, PI). I completed Task 2.a. by auditing Introduction to Genetic and Molecular Epidemiology with Drs. Xigeng Wu, Debbie del Junco and Corinne Aragaki at the University of Texas School of Public Health in Spring 2002 (Appendix G). I partially completed Task 2.c. by presenting the poster on "Adolescent soyfood intake, insulin-like growth factor-I and breast cancer risk" at the Society for Epidemiologic Research Meeting in June 2002.

During the third year of the study, I completed Task 1.b. by assisting Dr. R. Sue Day (formally McPherson) develop a course on Nutritional Epidemiology that I co-taught in Spring 2004 (Appendix H). I partially completed Task 1.c. by conducting analyses of dietary intake and anthropometric measurements of Behavioral Risk Factor Surveillance System data conducted on

the Texas-Mexico border. I partially completed Task 1.d. by working with Dr. Day and other members of the Lower Rio Grande Valley Nutrition Intervention Research Initiative (LRGVNIRI) consortium conducting analyses for a monograph on nutrition research and services in the LRGV. I completed Task 1.e. by receiving funding as Principal Investigator of the research institution for a HBCU/MI Partnership Award to the DOD to investigate insulin resistance and breast cancer (Appendix I contains the abstract). I completed Task 2.c. by conducting an oral presentation on "Soyfood intake, insulin-like growth factor-I and breast cancer risk" at the DOD Era of Hope Breast Cancer Research Program Meeting in September 2002, and by submitting a manuscript on this topic. I also completed Task 2.c. by publishing a letter entitled "Reply 1: An assessment of the preconceptional mitochondrial hypothesis" (Appendix J).

During the fourth year of the study, I partially completed Task 1.c. by submitting a MBRS SCORE grant (UTB, Dr. Gerson Peltz, PI) as consultant to expand the DOD-funded South Texas Women's Health Project to include urine collection and assessment of urinary excretion of phytoestrogen (Appendix K contains the abstract). I also partially completed Task 1.c. by publishing one paper entitled "Lifestyle and prostate cancer among older African-American and Caucasian men in South Carolina" (Appendix L) as first author and three cancer-related papers as co-author, and by providing data to the International Collaborative on Prenatal Factors and Breast Cancer. I partially completed Task 1.d. by working with Dr. Day and other members of the LRGVNIRI consortium conducting analyses for a monograph on nutrition research and services in the LRGV (Appendix M contains the cancer chapter). I completed Task 2.c. by publishing a paper entitled "Insulin-like growth factor-I, soyfood intake and breast cancer risk" (Appendix N). I completed Task 2.d. by collecting information and beginning to investigate dietary phytoestrogen intake, estrogen, insulin-like growth factor-I, insulin, glucose and breast cancer risk using the South Texas Women's Health Project. I partially completed Task 2.e. by acting as mentor on a NCI submission by Dr. Christine McCullum to investigate dietary intake and hormone levels in 4th grade girls (Appendix O contains the abstract).

During the fifth year of the study, Dr. Peltz and I received supplemental funding from DOD to add a urine collection and assessment of urinary phytoestrogen to the South Texas Women's Health Project. I completed Task 1.c. by conducting preliminary analyses of urinary phytoestrogen and breast cancer from the South Texas Women's Health Project; by publishing two papers entitled "Risk behaviors by ethnicity and Texas-Mexico border residence" (Appendix P) and "A multilevel analysis of socioeconomic status and prostate cancer risk" (Appendix Q) as first author; by publishing or presenting six other nutrition and/or cancer-related papers as co-author; by conducting an oral presentation on "Perinatal factors and mortality from breast cancer" (Appendix R) and co-authoring a poster presentation on "Use of mammography by Texas-Mexico border residence and ethnicity" (Appendix S) at the DOD Era of Hope Breast Cancer Research Program Meeting in June 2005, and by attending the International Collaborative on Prenatal Factors and Breast Cancer meeting in London in September 2005. I completed Task 1.d. by validating the phytoestrogen food frequency questionnaire used for the South Texas Women's Health Project with urinary excretion of phytoestrogen. I completed Task 2.b. by attending the American College of Epidemiology workshop on genetic epidemiology taught by Dr. Jack Taylor (Appendix T). I completed Task 2.e. by submitting a grant to follow a cohort of children of gestational diabetics from birth through age 12 years to investigate hormone levels in cord blood and subsequent childhood weight, height, diet and physical activity (Appendix U contains the abstract).

Key Research Accomplishments

- Completed Task 1.a. by auditing Pathology of Neoplasia.
- Completed Task 1.b. by assisting Dr. R. Sue Day (formally McPherson) develop a course on Nutritional Epidemiology that I co-taught.
- Completed Task 1.c. by publishing six nutrition and/or cancer papers as first author, and by publishing or presenting nine papers as co-author.
- Completed Task 1.c. by providing data to and attending the International Collaborative on Prenatal Factors and Breast Cancer.
- Completed Task 1.c. by obtaining supplemental funding to expand our DOD-funded South Texas Women's Health Project to include urine collection and urinary excretion of phytoestrogen.
- Completed Task 1.c. by conducting preliminary analyses of urinary phytoestrogen and breast cancer from the South Texas Women's Health Project.
- Completed Task 1.c. by conducting oral presentations at the DOD Era of Hope Breast Cancer Research Program Meeting in 2002 and 2005.
- Completed Task 1.d. by working with Dr. Day and other members of the LRGVNIRI consortium conducting analyses for a monograph on nutrition research and services in the Lower Rio Grande Valley.
- Completed Task 1.d. by validating the phytoestrogen food frequency questionnaire used for the South Texas Women's Health Project with urinary excretion of phytoestrogen.
- Completed Task 1.e. by receiving funding as Principal Investigator of the research institution on a HBCU/MI Partnership Award from the DOD to investigate insulin resistance and breast cancer.
- Completed Task 2.a. by auditing Introduction to Genetic and Molecular Epidemiology.
- Completed Task 2.b. by attending the Seattle Epidemiologic and Biostatistical Summer Session on genetic epidemiology.
- Completed Task 2.c. by presenting and publishing on the interaction between insulin-like growth factor-I, soyfood intake and breast cancer risk using data from the Shanghai Breast Cancer Study.
- Completed Task 2.d. by collecting information and beginning to investigate dietary phytoestrogen intake, estrogen, insulin-like growth factor-I, insulin, glucose and breast cancer risk using the South Texas Women's Health Project.

- Completed Task 2.e. by submitting a grant to follow a cohort of children of gestational diabetics from birth through age 12 years to investigate hormone levels in cord blood and subsequent childhood weight, height, diet and physical activity.

Reportable Outcomes

1) Manuscripts

Adegoke OJ, Blair A, Shu XO, Sanderson M, Jin F, Dosemeci M, Addy CL, Zheng W. Occupational history and exposure and the risk of adult leukemia in Shanghai. Ann Epidemiol 2003;13:485-494.

Adegoke OJ, Blair A, Shu XO, Sanderson M, Addy CL, Dosemeci M, Zheng W. Agreement of job-exposure matrix (JEM) assessed exposure and self-reported exposure among adult leukemia patients and controls in Shanghai. Am J Ind Med 2004;45:281-288.

Adegoke OJ, Shu XO, Linet M, Sanderson M, Addy CL, Jin F, Zheng W. Smoking, drinking and hair-dye use in relation to the risk of adult leukemia. Oncol Rep (In Press).

Coker AL, Sanderson M, Zheng W, Fadden MK. Diabetes Mellitus and Prostate Cancer Risk among Older Men: Population-based Case-Control Study. Br J Cancer 2004;90:2171-2175.

Coker AL, Sanderson M, Fadden MK. Psychosocial stress, coping and prostate cancer. Ethnicity Dis (In Press).

Du XL, *Fang S*, Coker AL, Sanderson M, Aragaki C, Cormier JN, Xing Y, Gor BJ, Chan W. Racial disparity and socioeconomic status in association with survival in older men with local/regional stage prostate cancer: Findings from a large community-based cohort. Cancer 2006;106:1276-1285.

Hebert JR, Gupta PC, Bhonsle RB, Mehta H, Zheng W, Sanderson M, Teas J. Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India. Public Health Nutr 2002;5:303-312.

Perez A, Reininger BM, Aguirre Flores MI, Sanderson M, Roberts RE. Physical activity and overweight among adolescents on the Texas-Mexico border. Pan American J Public Health (In Press).

Sanderson M, Shu X-O, Jin F, Dai Q, Wen W-Q, Hui Y, Gao Y-T, Zheng W. Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study. Int J Cancer 2001;92:899-905.

Sanderson M, Shu XO, Jin F, Dai Q, Ruan Z, Gao Y-T, Zheng W. Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population. Br J Cancer 2002;86:84-88.

Sanderson M, Shu XO, Zheng W. Reply 1: An assessment of the preconceptional mitochondrial hypothesis. Br J Cancer 2003;88:1819-1820.

Sanderson M, Shu XO, Yu H, Malin AS, Dai Q, Gao YT, Zheng W. Insulin-like growth factor-I, soyfood intake and breast cancer risk. Nutr Cancer 2004;50:8-15.

Sanderson M, Coker AL, Logan P, Fadden MK, Zheng W. Lifestyle and prostate cancer among older African-American and Caucasian men in South Carolina. Cancer Causes Control 2004:15:647-655.

Sanderson M, Peltz G. Nutrition and Cancer. In: Nourishing the future: the case for community-based nutrition research in the Lower Rio Grande Valley. Houston, TX:University of Texas School of Public Health at Houston, August 2004.

Sanderson M, Fernandez ME, Dutton RJ, Ponder A, Sosa D, Peltz G. Risk behaviors by ethnicity and Texas-Mexico border residence. Ethnicity Dis 2006;16:514-520.

Sanderson M, Coker AL, Perez A, Du XL, Peltz G, Fadden MK. A multilevel analysis of socioeconomic status and prostate cancer risk. Ann Epidemiol (In Press).

2) Abstracts/Presentations (exclusive of manuscripts)

Aragaki CC, Sanderson M, Coker A, Cai Q, Hayes R, Zheng W. Aryl hydrocarbon receptor SNP AHR modifies the effect of pesticide use on prostate cancer in South Carolina. Am J Epidemiol 2005;161:S95.

Meyer TE, Coker AL, Sanderson M, Symanski E. Reduction of exposure misclassification in a case-control study of farming-related exposures and prostate cancer. Am J Epidemiol 2005;161:S1.

Peltz G, Sanderson M, Perez A, Estrada JK, Johnson M. Use of mammography by Texas-Mexico border residence and ethnicity. 4th Department of Defense Breast Cancer Research Program Meeting, Philadelphia, PA, June 2005.

Sanderson M, Shu XO, Jin F, Dai Q, Yu H, Gao YT, Zheng W. Insulin-like growth factor-I, soyfood intake and breast cancer risk. 3rd Department of Defense Breast Cancer Research Program Meeting, Orlando, FL, September 2002.

Sanderson M, Daling JR, Malone KE, Doody DR, Porter PL. Perinatal factors and mortality from breast cancer. 4th Department of Defense Breast Cancer Research Program Meeting, Philadelphia, PA, June 2005.

3) Grants

Grant Name:	Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer
Funding Agency:	U.S. Army Medical Research and Materiel Command
Period of Funding:	April 1, 2001 – March 31, 2006 ($898,009)
Role:	Principal Investigator (20% effort years 1-5, 0% support years 1-3)

Grant Name:	Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women
Funding Agency:	U.S. Army Medical Research and Materiel Command
Period of Funding:	September 1, 2003 – August 31, 2007
Role:	Principal Investigator of UTSPH subcontract (20% effort years 1-4, 0% support years 1-2)

Grant Name:	Urinary Excretion of Phytoestrogen and Breast Cancer among Hispanic Women
Funding Agency:	National Institute of General Medical Sciences
Period of Funding:	September 1, 2004 – August 31, 2006
Role:	Consultant (2% effort)

Grant Name:	Hormones, Growth Factors, and Lipids among Gestational Diabetics and Their Infants
Funding Agency:	National Institute of Diabetes, Digestive and Kidney Disease
Period of Funding:	December 1, 2006 – November 30, 2008
Role:	Principal Investigator (20% effort)

Conclusions

To date, my breast cancer research has focused on surrogate markers of intrauterine exposure to estrogen and subsequent breast cancer (Appendix V contains my curriculum vitae). This research has led me to the understanding that prenatal and postnatal growth represent critical periods in breast carcinogenesis, in large part due to exposure to estrogen and other hormones/growth factors. Clearly, dietary intake is associated with prenatal and postnatal growth. Diet also has been related to estrogen, insulin-like growth factor-I (IGFI) and other hormones/growth factors, and to breast cancer. Elevated levels of IGFI and insulin, and abdominal obesity are markers for insulin resistance, which has been positively associated with breast cancer in several studies.

This Career Development Award investigated an area of recent interest in breast cancer, the interrelationships of prenatal and postnatal growth, hormones, diet, and breast cancer. The possibility that insulin resistance may tie these factors together led to my goal of studying the association between insulin resistance and breast cancer. A secondary goal was to assess the influence of genetic susceptibility, diet and physical activity on this association.

The Lower Rio Grande Valley (LRGV) of Texas is an exceptional location to perform breast cancer research because 85 percent of the population is Hispanic. Hispanic women in the LRGV have a relatively low incidence of breast cancer compared with non-Hispanic white women. In comparison with Hispanic women in the US, Hispanic women residing in the LRGV have a higher mortality from breast cancer. In contrast, Hispanic women are at greater risk of insulin resistance. This research allowed us to investigate whether the reduced risk of breast cancer among Hispanic women in the LRGV may be related to their higher genetic susceptibility to insulin resistance. Women tend to develop insulin resistance if they are genetically susceptible, gain excess weight due to physical inactivity, and consume a high-fat, low-fiber diet

during adolescence and adulthood. It is clear that this area of research has promise with regard to explaining the different breast cancer incidence and mortality rates by ethnicity.

In summary, the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer are complex. There is compelling evidence that insulin resistance may tie these relationships together, and may help explain the elevated risk of breast cancer among certain ethnic groups in the US. Should insulin resistance prove to be associated with breast cancer, the possibility that genetic susceptibility and adolescent/adult diet and physical activity may modify this association will be useful in targeting interventions for women at high risk for breast cancer.

References

Adegoke OJ, Blair A, Shu XO, Sanderson M, Jin F, Dosemeci M, Addy CL, Zheng W. Occupational history and exposure and the risk of adult leukemia in Shanghai. Ann Epidemiol 2003;13:485-494.

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Sanderson M, Coker AL, Perez A, Du XL, Peltz G, Fadden MK. A multilevel analysis of socioeconomic status and prostate cancer risk. Ann Epidemiol (In Press).

Statement of Work

Interrelationships of Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer

Task 1. Undergo intensive training in cancer biology and nutritional epidemiology, and conduct case-control studies of the insulin resistance-breast cancer relationship, Months 1-24:

a. Audit course in the pathology of neoplasia taught by Dr. Kim Creek
b. Audit course in nutritional epidemiology taught by Dr. R. Sue McPherson
c. In collaboration with Dr. R. Sue McPherson, assess nutritional status and physical activity, and conduct nutritional analyses of dietary intake, biochemical indicators and anthropometric measurements using her ongoing studies at the University of Texas School of Public Health at Houston
d. In collaboration with Dr. R. Sue McPherson, conduct analyses and prepare a manuscript for a validation study of a food frequency questionnaire used in her ongoing studies at the University of Texas School of Public Health at Houston
e. In collaboration with senior colleagues, submit grants to investigate the association between insulin resistance and breast cancer using an ongoing case-control study, the Shanghai Breast Cancer Study (R01-CA64277, PI Zheng) of 1500 cases and 1500 controls

Task 2. Undergo intensive training in molecular and genetic epidemiology, and conduct a cohort study of the association between prenatal and postnatal growth and infant hormone levels, Months 25-48:

a. Audit course in molecular epidemiology taught by Dr. Corinne Aragaki
b. Attend the Harvard University summer course in genetic epidemiology taught by Dr. Melissa Austin
c. In collaboration with Dr. Xiao Ou Shu, conduct analyses and prepare a manuscript investigating whether adolescent/adult diet and physical activity modifies the effect of estrogen and insulin-like growth factor 1 (IGF1) on breast cancer using a recently funded ancillary study from the Shanghai Breast Cancer Study
d. In collaboration with Dr. Wei Zheng, conduct analyses and prepare a manuscript investigating whether genetic susceptibility and adolescent/adult diet and physical activity modify the effect of estrogen, IGF1, insulin and C-peptide on breast cancer among women in Shanghai
e. In collaboration with senior colleagues, submit a grant to conduct a cohort study of 800 mothers and their female infants to investigate the association between maternal age, diet, preeclampsia, and infant birth weight, and hormone levels using the infants' cord blood; children will be followed for 12 years and childhood/adolescent weight, height, diet and physical activity will be assessed at 4-year intervals

Syllabus: Pathology of Neoplasia

Pathology 710
Tuesdays and Thursdays from 3:30 – 5:00
Department of Microbiology and Immunology Conference Room
Building 2, Room C4
(28 Class Periods)

Faculty: Kim E. Creek, Ph.D., will serve as course coordinator.
Office, Building 4, Room C7
Phone: 733-3153
Email: creek@med.sc.edu

Neoplasia will be a "team" taught course bringing together the considerable expertise in cancer biology that exists within the USC community. Each instructor will present information in their area of expertise. The format of presentation, as well as the material to be presented, is entirely up to each faculty member participating in the course.

Background: This is a required course of all graduate students who wish to specialize in the Molecular Oncology Focus Area and will usually be taken by students entering their second year of study. Since all students in this course have a strong interest in oncology, the course will be taught at a level to provide students with the most up-to-date information possible and at a level appropriate for students in their second year of graduate study. The topics to be presented cover most areas of neoplasia and the basic science of oncology. We realize that it is impossible in a one semester course to cover all aspects of this extremely large and broad topic. However, we will emphasize the topics and areas that I believe are most appropriate for graduate students in a Biomedical Sciences Program.

Textbook: The required textbook for the course is "*The Basic Science of Oncology*" 3rd Edition, by I.F. Tannock and R.P. Hill, 1998. The book is available for purchase in the School of Medicine bookstore. Additional reference books are: "*The biological Basis of Cancer*" by R.G. McKinnell, R.E.Parchment, A.O. Perantoni, and G.B. Pierce, 1998 and "*Introduction to the Cellular and Molecular Biology of Cancer*" 3rd Edition, by L.M. Franks and N.M. Teich, 1997.

The following web site http://www.carcin.oupjournals.org/content/vol21/issue3/ has the full text of a recent issue of the journal *Carcinogenesis* that contains several review articles on various aspects of cancer biology. This should serve as a valuable source f very current information.

Grading: The final grade will be based on two "take-home" exams (50% each exam), consisting of questions supplied by the various instructors. The exact dates of the exams will be announced in class.

Schedule of Lectures

August 24 Introduction to Course (Creek)

August 29 Overview of Neoplasia (Lill)

August 31 Overview of Neoplasia (Lill)

September 5 Tumor Nomenclature (Lill)

September 7 Mechanisms of Metastasis (Lill)

September 12 Viral Carcinogenesis (Pirisi)

September 14 Viral Carcinogenesis (Pirisi)

September 19 Chemical Carcinogenesis (Farber)

September 21 Chemical Carcinogenesis (Farber)

September 26 Multistep Nature of Cancer (Farber)

September 28 Cell Cycle (Pirisi)

October 3 Oncogenes/Apoptosis/Telomerase (Patton)

October 5 Tumor Suppressor Genes (Patton)

October 10 Growth Factors/Signaling Pathways in Cancer (Creek)

October 12 Growth Factors/Signaling Pathways in Cancer (Creek)

October 17 No Class (Fall Break)

October 19 Epidemiology of Cancer (Maureen Sanderson)

October 24 Hormones and Cancer (Housley)

October 26 Hormones and Cancer (Housley)

October 31 Breast Cancer (Cunningham)

November 2 Prostate Cancer (Bostick)

November 7 No Class (Election Day)

November 9 Colon Cancer (Wargovich)

November 14 Chemoprevention (Wargovich)

November 16 Diet and Cancer (Wargovich)

November 21 Immunology of Cancer (Lamb)

November 23 No Class (Thanksgiving)

November 28 Molecular Epidemiology (Dawen)

November 30 Principles of Chemotherapy (Spencer)

December 5 Immunotherapy (Spencer)

December 7 Gene Therapy (Spencer)

Manuscript: Sanderson M, Shu X-O, Jin F, Dai Q, Wen W-Q, Hui Y, Gao Y-T, Zheng W. Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study. Int J Cancer 2001;92:899-905.

Int. J. Cancer: **92,** 899–905 (2001)

Publication of the International Union Against Cancer

ABORTION HISTORY AND BREAST CANCER RISK: RESULTS FROM THE SHANGHAI BREAST CANCER STUDY

Maureen SANDERSON[1]*, Xiao-Ou SHU[1,2], Fan JIN[3], Qi DAI[1–3], Wanqing WEN[1,2], Yi HUA[3], Yu-Tang GAO[3] and Wei ZHENG[1,2]

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Studies of the association between induced abortion and breast cancer risk have been inconsistent, perhaps due to underreporting of abortions. Induced abortion is a well-accepted family planning procedure in China, and women who have several induced abortions do not feel stigmatized. The authors used data from a population-based case-control study of breast cancer among women age 25–64 conducted between 1996 and 1998 in urban Shanghai to assess whether a history of and the number of induced abortions were related to breast cancer risk. In-person interviews were completed with 1,459 incident breast cancer cases ascertained through a population-based cancer registry, and 1,556 controls randomly selected from the general population in Shanghai (with respective response rates of 91% and 90%). After adjusting for confounding, there was no relation between ever having had an induced abortion and breast cancer (odds ratio [OR] = 0.9, 95% confidence interval [CI] 0.7–1.2). Women who had 3 or more induced abortions were not at increased risk of premenopausal breast cancer (OR = 0.9, 95% CI 0.6–1.4) or postmenopausal breast cancer (OR = 1.3, 95% CI 0.8–2.3). These results suggest that a history of several induced abortions has little influence on breast cancer risk in Chinese women.

Key words: *abortion; breast cancer; pregnancy; case-control studies*

Studies of induced abortion and breast cancer risk have been inconsistent. Underreporting of induced abortion is suspected,[1] which may be reflected in the low reported percentages of women who had undergone the procedure in these studies. In the majority of previous studies of this association fewer than 20% of women have reported induced abortions. The Iowa Women's Health Study, a cohort study, had the lowest percentage of reported induced abortions (2%), and found no association between induced abortion and breast cancer risk (OR = 1.1, 95% CI 0.8–1.6).[2] An intermediate percentage of reported induced abortions (39%) was found in a Greek case-control study that reported an elevated risk of breast cancer associated with induced abortion (OR = 1.51, 95% CI 1.28–1.84).[3] The highest percentage of reported induced abortions (76%) was seen in a Russian case-control study that reported no association for 1 abortion (OR = 1.0, 95% CI 0.7–1.4) and a borderline reduced risk for 2 or more abortions (OR = 0.7, 95% CI 0.6–1.0).[4] Remennick[5] postulated that should induced abortion be related to breast cancer Russian women may be at a greater risk given the extremely frequent use of the procedure. The same may be true of women in China that had 1 of the highest induced abortion rates in the world during the childbearing years for the majority of women in this study.[6]

This study was conducted to assess whether a history of and the number of induced abortions were related to breast cancer risk. The lack of social stigma associated with induced abortion in China may limit the amount of underreporting of the procedure and present a clearer picture of this association.

MATERIAL AND METHODS

Detailed methods of this population-based case-control study appear elsewhere.[7] Briefly, all women age 25–64 years who were permanent residents of urban Shanghai at the time of diagnosis of first primary invasive breast cancer (August 1996 through March 1998) were eligible for the study. Two senior pathologists histologically confirmed all diagnoses. We used rapid case ascertainment supplemented by the Shanghai Cancer Registry to identify breast cancer cases who had no prior history of cancer and were alive at the time of interview. A total of 1,459 breast cancer cases (91.1% of eligible cases) completed a standardized in-person interview. Of eligible cases, 109 refused (6.8%), 17 died before the interview (1.1%), and 17 were not located (1.1%).

The Shanghai Resident Registry, a listing of all permanent residents of urban Shanghai, was used to randomly select controls. Controls were frequency matched to cases on age (5-year interval) based on the number of incident breast cancer cases by age group reported to the Shanghai Cancer Registry from 1990–1993. Women who did not reside at the registered address at the time of the study were ineligible. A total of 1,556 controls (90.4% of eligible controls) completed a standardized in-person interview. The remaining 166 eligible controls (9.6%) refused participation. Two women died before the interview and were excluded. Over 95% of women had a live birth, therefore we restricted this analysis to parous women (1,385 cases, 1,495 controls).

The study was approved by a local institutional review board. Women were interviewed at hospitals (cases) or at home (cases and controls) by trained interviewers. The questionnaire collected information on demographic factors, reproductive and medical histories, family history of cancer, use of oral contraceptives or hormone replacement therapy, diet, physical activity, lifestyle factors, and body size. Women provided detailed information on each pregnancy, including its outcome and gestational length. After completing the interview, women were weighed and had their standing and sitting height, and waist and hip circumferences measured. Women were classified as premenopausal if they reported having menstrual periods within the past 12 months. Postmenopausal women were those who had undergone natural or surgical menopause. Information on exposures pertained to the period before an assigned reference date, the diagnosis date for breast cancer cases and a similar date for controls.

We used unconditional logistic regression to estimate the relative risk of breast cancer associated with abortion history while controlling for confounders.[8] All variables other than age (continuous) were entered into models as dummy variables. Variables were considered confounders of the relationship be-

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TABLE I – COMPARISON OF CASES AND CONTROLS ON BREAST CANCER RISK FACTORS

	Cases (n = 1,385)		Controls (n = 1,495)		OR	(95% CI)	Age-adjusted	
	No.	%	No.	%			OR	(95% CI)
Age (years)								
25–34	37	2.7	69	4.6	1.0	(reference)		
35–44	494	35.7	551	36.9	1.7	(1.1–2.5)		
45–54	538	38.8	497	33.2	2.0	(1.3–3.1)		
55–64	316	22.8	378	25.3	1.6	(1.0–2.4)		
Education								
Never	51	3.7	84	5.6	1.0	(reference)	1.0	(reference)
Elementary	118	8.5	127	8.5	1.5	(1.0–2.4)	1.6	(1.0–2.5)
Middle + High	1,036	74.8	1,130	75.6	1.5	(1.0–2.2)	1.9	(1.3–2.8)
Prof. + College	180	13.0	154	10.3	1.9	(1.3–2.9)	2.2	(1.5–3.4)
Per capita income (last year, yuan)								
<4,000	261	18.9	276	18.5	1.0	(reference)	1.0	(reference)
4,000–5,999	450	32.5	485	32.5	1.0	(0.8–1.2)	1.0	(0.8–1.3)
6,000–7,999	180	13.0	208	13.9	0.9	(0.7–1.2)	0.9	(0.7–1.2)
8,000–8,999	280	20.2	346	23.1	0.9	(0.7–1.1)	0.9	(0.7–1.1)
≥9,000	213	15.4	180	12.0	1.3	(1.0–1.5)	1.3	(1.0–1.7)
Breast cancer among first-degree relatives								
No	1,333	96.3	1,459	97.6	1.0	(reference)	1.0	(reference)
Yes	52	3.7	36	2.4	1.6	(1.0–2.4)	1.6	(1.0–2.4)
Ever had breast fibroadenoma								
No	1,253	90.5	1,422	95.1	1.0	(reference)	1.0	(reference)
Yes	131	9.5	73	4.9	2.0	(1.5–2.7)	2.1	(1.5–2.8)
Age at menarche (years)								
10–12	128	9.3	123	8.2	1.0	(reference)	1.0	(reference)
13–16	1,115	80.5	1,150	77.0	0.9	(0.7–1.2)	0.9	(0.7–1.2)
≥17	141	10.2	221	14.8	0.6	(0.4–0.9)	0.6	(0.4–0.8)
Menopause								
No	903	65.4	949	63.6	1.0	(reference)	1.0	(reference)
Yes	478	34.6	543	36.4	0.9	(0.8–1.1)	0.6	(0.5–0.8)
Age at menopause								
<45	77	16.1	116	21.6	1.0	(reference)	1.0	(reference)
45–49	203	42.6	219	40.7	1.4	(1.0–2.0)	1.5	(1.0–2.1)
≥50	197	41.3	203	37.7	1.5	(1.0–2.1)	1.6	(1.1–2.3)
Body mass index (by quartile)								
≤20.70	281	20.3	373	25.0	1.0	(reference)	1.0	(reference)
20.71–22.79	331	24.0	373	25.0	1.2	(1.0–1.5)	1.2	(0.9–1.5)
22.80–25.10	373	27.0	376	25.1	1.3	(1.1–1.6)	1.3	(1.0–1.6)
>25.10	397	28.7	372	24.9	1.4	(1.2–1.8)	1.4	(1.1–1.7)
Waist-to-hip ratio (by quartile)								
≤0.764	265	19.2	373	25.0	1.0	(reference)	1.0	(reference)
≤0.765–0.800	351	25.4	398	26.6	1.2	(1.0–1.5)	1.2	(1.0–1.5)
0.801–0.835	348	25.2	345	23.1	1.4	(1.1–1.8)	1.4	(1.1–1.7)
>0.835	418	30.2	378	25.3	1.6	(1.3–1.9)	1.5	(1.2–1.9)
Alcohol consumption								
Never	1,329	96.1	1,432	96.0	1.0	(reference)	1.0	(reference)
Ever	54	3.9	60	4.0	1.0	(0.7–1.4)	1.0	(0.7–1.4)
Oral contraceptive use								
Never	1,068	77.1	1,172	78.4	1.0	(reference)	1.0	(reference)
Ever	317	22.9	323	21.6	1.1	(0.9–1.3)	1.0	(0.9–1.2)
Physical activity during past 10 years								
Never	1,128	81.5	1,117	74.8	1.0	(reference)	1.0	(reference)
Ever	256	18.5	377	25.2	0.7	(0.6–0.8)	0.6	(0.5–0.7)
Age at first live birth								
<20	62	4.5	73	4.9	1.0	(reference)	1.0	(reference)
20–24	303	21.9	360	24.1	1.0	(0.7–1.4)	1.1	(0.8–1.6)
25–29	712	51.4	816	54.6	1.0	(0.7–1.5)	1.3	(0.9–1.8)
30–34	248	17.9	206	13.7	1.4	(1.0–2.1)	1.7	(1.1–2.6)
35+	60	4.3	40	2.7	1.8	(1.1–3.0)	2.1	(1.2–3.6)
Number of live births								
1	912	65.9	975	65.2	1.0	(reference)	1.0	(reference)
2	317	22.9	333	22.3	1.0	(0.9–1.2)	0.8	(0.6–1.0)
3	104	7.5	121	8.1	0.9	(0.7–1.2)	0.6	(0.4–0.9)
≥4	52	3.7	66	4.4	0.8	(0.6–1.2)	0.5	(0.4–0.8)
Cumulative duration of breastfeeding								
No	302	21.8	300	20.1	1.0	(reference)	1.0	(reference)
1–11 months	593	42.8	638	42.7	0.9	(0.8–1.1)	0.9	(0.8–1.1)
12–23 months	275	19.9	307	20.5	0.9	(0.7–1.1)	0.8	(0.6–1.0)
≥24 months	215	15.5	250	16.7	0.9	(0.7–1.1)	0.7	(0.5–0.9)
Stillbirth								
Never	1,357	98.0	1,472	98.5	1.0	(reference)	1.0	(reference)
Ever	28	2.0	23	1.5	1.3	(0.8–2.3)	1.3	(0.8–2.3)

TABLE II – ODDS RATIOS OF BREAST CANCER ASSOCIATED WITH INDUCED ABORTION

	Premenopausal women			Postmenopausal women		
	Case/ctrl	OR[1]	(95% CI)	Case/ctrl	OR[1]	(95% CI)
Abortion						
Never	283/292	1.0	(reference)	188/209	1.0	(reference)
Ever	620/657	1.0	(0.8–1.2)	290/334	0.9	(0.7–1.2)
Number of abortions						
1	404/394	1.1	(0.9–1.3)	152/206	0.8	(0.6–1.1)
2	170/215	0.8	(0.6–1.0)	100/97	1.0	(0.7–1.5)
≥3	46/48	0.9	(0.6–1.4)	38/31	1.3	(0.8–2.3)
		$p = 0.13$			$p = 0.50$	
Age at first abortion (years)						
<25	40/69	0.7	(0.4–1.0)	41/35	1.1	(0.7–1.9)
25–29	296/328	1.0	(0.8–1.2)	113/144	0.8	(0.6–1.2)
30–34	205/179	1.1	(0.9–1.5)	95/115	0.9	(0.6–1.3)
≥35	77/81	0.9	(0.6–1.3)	41/39	1.1	(0.7–1.8)
		$p = 0.39$			$p = 0.57$	
Time of first abortion						
Before first live birth	72/86	1.0	(0.7–1.4)	11/13	0.9	(0.4–2.1)
After first live birth	548/571	1.0	(0.8–1.2)	279/321	0.9	(0.7–1.2)
Number of abortions relative to first live birth						
Before first live birth						
1	64/76	1.0	(0.7–1.5)	9/13	0.7	(0.3–1.8)
≥2	8/10	1.0	(0.4–2.7)	2/0	—	
		$p = 0.81$			$p = 0.70$	
After first live birth						
1	368/360	1.1	(0.8–1.3)	147/202	0.8	(0.6–1.1)
2	139/173	0.8	(0.6–1.0)	96/91	1.0	(0.7–1.5)
≥3	41/38	0.9	(0.6–1.5)	36/28	1.4	(0.8–2.5)
		$p = 0.12$			$p = 0.09$	
Interval between first abortion and reference date (years)						
0–9	126/167	1.0	(0.7–1.4)	5/4	1.9	(0.5–8.0)
10–14	209/251	0.9	(0.7–1.2)	15/19	0.9	(0.4–1.9)
15–19	171/143	1.1	(0.8–1.5)	31/32	1.1	(0.6–1.9)
≥20	112/96	0.8	(0.6–1.2)	239/278	0.9	(0.7–1.2)
		$p = 0.32$			$p = 0.78$	
Gestational length of first abortion (weeks)						
1–8	503/545	0.9	(0.8–1.2)	230/262	0.9	(0.7–1.2)
9–12	89/79	1.2	(0.8–1.7)	45/57	0.9	(0.6–1.4)
≥13	25/32	0.9	(0.5–1.6)	14/14	1.3	(0.6–2.9)
		$p = 0.50$			$p = 0.43$	

[1]Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, age at menopause, waist-to-hip ratio, physical activity, duration of breastfeeding, spontaneous abortion, age at first live birth, and number of live births.

tween abortion history and breast cancer risk if their addition to the model changed the unadjusted odds ratio by 10% or more. Product terms between induced abortion and potential effect modifiers were added to the model to assess departure from a multiplicative relation. In multiple logistic regression models, we assessed linear trend by treating categorical variables as continuous variables.

RESULTS

Table I presents odds ratios (OR) and 95% confidence intervals (CI) for known breast cancer risk factors comparing cases and controls unadjusted and adjusted for age. Breast cancer cases were more likely than controls to be older, more highly educated, have a first-degree relative with breast cancer, have a history of fibroadenoma, have an earlier age at menarche, be premenopausal, have a later age at menopause, have a higher body mass index, have a higher waist-to-hip ratio, have a later age at first birth, and have fewer live births. Cases were less likely than controls to engage in physical activity and to have breast fed for 12 months or more. With the exception of age, none of the preceding variables were confounders of the association between induced abortion and breast cancer. Adjustment was made for these variables, however, to be consistent with the majority of studies on this topic. In addition, the induced abortion analyses are adjusted for a history of spontaneous abortion, and the spontaneous abortion analyses are adjusted for a history of induced abortion. Although there was no evidence of effect modification, analyses are presented separately by menopausal status because the effect of some hormonal exposures on breast cancer risk is thought to differ by menopausal status.

Table II shows results for the induced abortion and breast cancer association stratified by menopausal status. The percentage of women who had an induced abortion was slightly higher among premenopausal women (69% of cases and controls) than among postmenopausal women (61% of cases and 62% of controls). After adjusting for confounding, there was no overall relation between ever having had an induced abortion and breast cancer (OR = 1.0, 95% CI 0.8–1.2). Women who had 3 or more induced abortions were not at increased risk of premenopausal breast cancer (OR = 0.9, 95% CI 0.6–1.4) or postmenopausal breast cancer (OR = 1.3, 95% CI 0.8–2.3). Among premenopausal and postmenopausal women, there was little effect on breast cancer risk of age at first induced abortion, timing of first induced abortion relative to timing of first live birth, number of induced abortions relative to timing of first live birth, interval between first induced abortion and reference date, or gestational length of first induced abortion.

In analyzing the number of induced abortions and the age at first induced abortion by menopausal status, we stratified by age at first live birth and number of live births (Table III). Among premenopausal women, the effect of having 3 or more induced abortions differed by age at first live birth (≤25 years: OR = 0.5, 95% CI 0.2–1.1; >25 years: OR = 1.4, 95% CI 0.8–2.5). Postmenopausal women who had 3 or more induced abortions and 2 or more live

TABLE III – ODDS RATIOS OF BREAST CANCER ASSOCIATED WITH INDUCED ABORTION BY CHARACTERISTICS OF LIVE BIRTH

	Premenopausal women					
	Age at first live birth (years)					
	≤25 years			>25 years		
	Case/ctrl	OR[1,2]	(95% CI)	Case/ctrl	OR[1,2]	(95% CI)
Number of abortions						
0	49/61	1.0	(reference)	234/231	1.0	(reference)
1	94/92	1.3	(0.8–2.2)	310/302	1.0	(0.8–1.3)
2	61/76	1.0	(0.6–1.6)	109/139	0.8	(0.6–1.1)
≥3	14/26	0.5	(0.2–1.1)	32/22	1.4	(0.8–2.5)
Age at first abortion (years)						
<25	48/61	1.0	(reference)	234/231	1.0	(reference)
25–29	56/82	0.9	(0.5–1.6)	17/21	1.0	(0.5–2.0)
30–34	90/92	1.2	(0.7–1.9)	236/258	0.9	(0.7–1.2)
≥35	21/20	1.2	(0.6–2.6)	198/184	1.0	(0.8–1.3)
	Number of live births					
	1			≥2		
	Case/ctrl	OR[1,3]	(95% CI)	Case/ctrl	OR[1,3]	(95% CI)
Number of abortions						
0	253/266	1.0	(reference)	30/26	1.0	(reference)
1	360/358	1.1	(0.8–1.3)	44/36	1.2	(0.6–2.5)
2	130/180	0.7	(0.6–1.0)	40/35	1.2	(0.6–2.4)
≥3	39/39	1.0	(0.6–1.6)	7/9	0.6	(0.2–2.0)
	Postmenopausal women					
	Age at first live birth (years)					
	≤25 years			>25 years		
	Case/ctrl	OR[1,2]	(95% CI)	Case/ctrl	OR[1,2]	(95% CI)
Number of abortions						
0	114/142	1.0	(reference)	74/67	1.0	(reference)
1	88/125	0.9	(0.6–1.3)	64/81	0.7	(0.5–1.2)
2	59/70	1.0	(0.6–1.5)	41/27	1.3	(0.7–2.4)
≥3	23/19	1.4	(0.7–2.9)	15/12	1.1	(0.5–2.7)
Age at first abortion (years)						
<25	114/142	1.0	(reference)	74/67	1.0	(reference)
25–29	53/64	0.9	(0.6–1.5)	2/1	1.8	(0.1–23.9)
30–34	79/97	1.0	(0.7–1.5)	45/49	0.8	(0.5–1.4)
≥35	38/52	1.0	(0.6–1.6)	73/70	1.0	(0.6–1.6)
	Number of live births					
	1			≥2		
	Case/ctrl	OR[1,3]	(95% CI)	Case/ctrl	OR[1,3]	(95% CI)
Number of abortions						
0	54/38	1.0	(reference)	134/171	1.0	(reference)
1	49/61	0.5	(0.3–1.0)	103/145	1.0	(0.7–1.3)
2	17/24	0.5	(0.2–1.1)	83/73	1.4	(0.9–2.0)
≥3	8/7	0.8	(0.2–2.4)	30/24	1.8	(1.0–3.2)

[1]Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, age at menopause, waist-to-hip ratio, physical activity, duration of breastfeeding, and spontaneous abortion.–[2]Additionally adjusted for number of live births.–[3]Additionally adjusted for age at first live birth.

births had a borderline increased risk of breast cancer (OR = 1.8, 95% CI 1.0–3.2), however the confidence interval surrounding this point estimate is quite wide. The combination of age at first induced abortion and age at first live birth did not influence breast cancer risk.

Table IV presents the induced abortion and breast cancer relation stratified by menopausal status and lactation history. The percentages of women who breast-fed were slightly lower among premenopausal women (75% of cases, 73% of controls) than among postmenopausal women (85% of cases, 92% of controls). Lactation history had little effect on the induced abortion and breast cancer association among premenopausal women. Among postmenopausal women who had an induced abortion after their first live birth and had never breast-fed there seemed to be a reduced risk of breast cancer (OR = 0.3, 95% CI 0.1–0.8). Postmenopausal women who did breast-feed were not at reduced risk of breast cancer.

The spontaneous abortion and breast cancer association is presented in Table V for comparison with the induced abortion and breast cancer relations. Much smaller percentages of women had spontaneous abortions than had induced abortions (premenopausal: 9% of cases, 8% of controls; postmenopausal: 14% of cases, 17% of controls). There was no overall effect of spontaneous abortion on breast cancer risk (OR = 0.9, 95% CI 0.7–1.2). There was a suggestive decreasing risk with increasing number of spontaneous abortions among postmenopausal women (trend test $p = 0.08$). Premenopausal women were at increasing risk of breast cancer associated with increasing age at first spontaneous abortion (trend test $p = 0.04$). Although not significant, the effect of increasing interval between first spontaneous abortion and reference date seemed to be associated with decreasing breast cancer risk among premenopausal (trend test $p = 0.07$) and postmenopausal women (trend test $p = 0.10$). Gestational length of first spontaneous abortion was not associated with breast cancer risk.

TABLE IV – ODDS RATIOS OF BREAST CANCER ASSOCIATED WITH INDUCED ABORTION BY LACTATION HISTORY

Lactation	Induced abortion	Case	Control	OR[1]	(95% CI)
Premenopausal women					
Never	No abortion	78	87	1.0	(reference)
	Yes, before first live birth	29	26	1.4	(0.8–2.6)
	Yes, after first live birth	121	144	0.9	(0.6–1.3)
Ever	No abortion	205	205	1.0	(reference)
	First abortion before first live birth	45	60	0.8	(0.5–1.3)
	First abortion ≤2 years before live birth	21	21	1.3	(0.7–2.5)
	First abortion >2 years before live birth	24	39	0.7	(0.4–1.2)
	First abortion after first live birth	425	428	1.0	(0.8–1.3)
	First abortion ≤2 years after live birth	275	287	1.0	(0.7–1.3)
	First abortion 2–5 years after live birth	97	82	1.1	(0.8–1.6)
	First abortion >5 years after live birth	53	58	0.8	(0.5–1.2)
Postmenopausal women					
Never	No abortion	36	10	1.0	(reference)
	Yes, before first live birth	5	4	0.2	(0.04–1.2)
	Yes, after first live birth	33	29	0.3	(0.1–0.8)
Ever	No abortion	152	199	1.0	(reference)
	First abortion before first live birth	6	10	0.9	(0.3–2.8)
	First abortion ≤2 years before live birth	1	0	—	
	First abortion >2 years before live birth	5	10	0.7	(0.2–2.1)
	First abortion after first live birth	247	291	1.1	(0.8–1.4)
	First abortion ≤2 years after live birth	82	90	1.2	(0.8–1.7)
	First abortion 2–5 years after live birth	81	86	1.2	(0.8–1.7)
	First abortion >5 years after live birth	85	115	1.0	(0.7–1.4)

[1]Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, age at menopause, waist-to-hip ratio, physical activity, spontaneous abortion, age at first live birth, and number of live births.

TABLE V – ODDS RATIOS OF BREAST CANCER ASSOCIATED WITH SPONTANEOUS ABORTION

	Premenopausal women			Postmenopausal women		
	Case/ctrl	OR[1]	(95% CI)	Case/ctrl	OR[1]	(95% CI)
Abortion						
Never	818/872	1.0	(reference)	411/451	1.0	(reference)
Ever	85/77	1.1	(0.8–1.6)	67/92	0.8	(0.5–1.1)
Number of abortions						
1	69/70	1.0	(0.7–1.5)	59/77	0.8	(0.6–1.2)
≥2	16/7	2.2	(0.9–5.5)	8/15	0.5	(0.2–1.3)
		$p = 0.24$			$p = 0.08$	
Age at first abortion (years)						
<25	9/12	0.8	(0.3–2.0)	23/36	0.7	(0.4–1.2)
25–29	51/52	1.0	(0.7–1.6)	26/35	0.8	(0.4–1.3)
30–34	19/13 [2]	1.7	(0.9–3.5)	15/17	0.9	(0.4–1.8)
≥35	6/0 [2]			3/4	0.8	(0.2–3.9)
		$p = 0.04$			$p = 0.51$	
Time of first abortion						
Before first live birth	70/68	1.1	(0.8–1.5)	28/36	0.8	(0.4–1.3)
After first live birth	15/9	1.6	(0.7–3.7)	39/56	0.8	(0.5–1.2)
Number of abortions relative to first live birth						
Before first live birth						
1	57/61	1.0	(0.7–1.4)	26/33	0.8	(0.4–1.3)
≥2	13/7	1.9	(0.7–4.8)	2/3	0.7	(0.1–4.1)
		$p = 0.65$			$p = 0.91$	
Interval between first abortion and reference date (years)						
0–9	10/11	1.4	(0.6–3.4)	1/0 [2]		
10–14	30/23	1.5	(0.9–2.7)	2/2 [2]	2.2	(0.4–14.0)
15–19	24/23	1.0	(0.6–1.9)	3/2	1.3	(0.2–8.0)
≥20	21/20	0.8	(0.4–1.5)	61/88	0.7	(0.5–1.0)
		$p = 0.07$			$p = 0.10$	
Gestational length of first abortion (weeks)						
1–8	46/35	1.3	(0.8–2.1)	28/37	0.8	(0.5–1.3)
9–12	26/29	1.0	(0.6–1.7)	21/38	0.6	(0.3–1.0)
≥13	13/13	0.9	(0.4–2.1)	16/17	1.0	(0.5–2.0)
		$p = 0.46$			$p = 0.17$	

[1]Adjusted for age, education, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, age at menopause, waist-to-hip ratio, physical activity, duration of breastfeeding, induced abortion, age at first live birth, and number of live births.–[2] Categories collapsed to calculate OR.

DISCUSSION

Our overall null association for breast cancer as it relates to induced abortion is in agreement with several recent case-control studies conducted among women of all age groups,[9–11] and restricted to younger women.[12–14] We are also in agreement with 2 recent cohort studies that reported relative risks of 1.0 (95% CI 0.94–1.06)[15] and 1.1 (95% CI 0.8–1.6),[2] respectively. Nor did we find an increased risk associated with several induced abortions. We compared our results with studies con-

ducted in countries where induced abortions are common, Russia, China and Japan. Our results are similar to 2 case-control studies,[16,17] but differ from 3 case-control studies that found elevated breast cancer risks associated with ever having had an induced abortion and with increasing number of induced abortions.[18–20] The studies that reported positive associations between induced abortion and breast cancer risk may have been limited by their failure to control for age at first birth,[18,20] or by their use of hospital-based cases and neighborhood controls.[19]

The 1 previous study of this association conducted in China has only appeared in abstract form.[19] Bu *et al.*[19] reported an elevated risk of early breast cancer among parous women who had an induced abortion (OR = 2.9, 95% CI 1.9–4.4), which was more pronounced among women who had 2 or more induced abortions (OR = 3.6, 95% CI 2.2–6.0). This increased risk is surprising because the majority of women in China have several induced abortions after a first live birth,[21] which is known to be protective against breast cancer.[7,22,23] The extremely high odds ratios reported for known breast cancer risk factors such as age at first birth older than 30 years (OR = 7.8, 95% CI 3.2–19.0) and family history of breast cancer (OR = 9.0, 95% CI 2.6–31.5) found in this study also raised concerns about the methodology used in this study.

The most common early abortion procedure used in China during the childbearing years of the majority of the women in the study was vacuum aspiration.[24] For women undergoing late abortions, intra-amniotic injections of abortifacients like rivanol or Traditional Chinese yuanhuacine were used.[25] After late abortions, a number of methods have been used to inhibit lactation including hormones, such as diethylstilbestrol (DES), dopamine agonists, and breast compression.[26] Because fewer than 5% of women in the present study had induced abortions after the first trimester, and the most common practice in China is to use Traditional Chinese topical ointments for lactation inhibition, it is unlikely that the use of hormones to inhibit lactation had much of an impact on breast cancer risk.

The biological mechanism that has been proposed to explain the increased risk of breast cancer associated with induced abortion in some studies pertains to the undifferentiated nature of breast cells during the first trimester of pregnancy among women without a full-term pregnancy.[27] In animal studies, Russo *et al.*[28] found that the breast tissue of rats whose pregnancy was terminated early began to proliferate, but did not differentiate as is done during a full-term pregnancy. These undifferentiated cells may become vulnerable to malignancy. Presumably, the greater number of induced abortions that occur before a full-term pregnancy the greater number of undifferentiated breast cells at risk of malignancy. This may help explain the elevated breast cancer risk with increasing number of abortions reported in Russia[18] and Japan,[20] because women in those countries tend to have several abortions before a first live birth. We, however, found no difference between first induced abortion occurring before or after the first live birth, in agreement with most studies of this topic,[11,29,30] although only a few women reported they had an abortion before the first live birth in our study population.

This study has many strengths. The population-based nature of the study and its extremely high response rates (cases: 91%; controls: 90%) minimizes selection bias. Underreporting of induced abortions is unlikely in our study given its' widespread use in China as a family planning method in case of contraceptive nonuse or failure.[21] China has had a series of family planning campaigns in place since 1956. Induced abortion was legalized in China in 1957 around the time most of the women in this study were beginning their childbearing years.[6] The procedure is free of charge and readily available. Because the primary method of family planning in China at the time most women in this study were using contraception was the intrauterine device that was known to have high failure rates and women were expected to have a child soon after marriage, women oftentimes had more than 1 abortion after the birth of their first or second child but not before their first live birth. Because of this and because Chinese women who have several induced abortions do not feel stigmatized, we believe that the information on abortion collected in our study is rather accurate. Our notion is supported by the findings of 3 recent studies of induced abortion in Shanghai,[31] Beijing[32] and 4 northern counties in China[33] that reported percentages of women with a history of induced abortion of approximately 60%, similar to the percentage seen in this study.

We adjusted for known breast cancer risk factors and evaluated the induced abortion-breast cancer association in conjunction with first live birth, lactation and number of pregnancies. Past studies of the induced abortion and breast cancer association have been limited by combining induced and spontaneous abortions, choosing an inappropriate reference group, failing to control for effect modification and confounding, and suspected underreporting of induced abortions among controls.[34,35] We analyzed induced and spontaneous abortions separately, and adjusted for the other outcome in the analysis. Because of the low rate of nulliparity and extremely low induced abortion rate among nulliparous women, our analysis was restricted to parous women, which prevented us from assessing whether the induced abortion and breast cancer relation was stronger among nulliparous than among parous women. The effect of some hormonal exposures on breast cancer risk is thought to differ by menopausal status,[36] therefore we presented our results separately by menopausal status even though there was no evidence of effect modification. In this low-risk country, only 54 cases and 38 controls had a first-degree family history of breast cancer preventing us from assessing its' role as an effect modifier.

In summary, our study indicates that a history of several induced abortions has little influence on breast cancer risk in Chinese women. Although we obtained relevant information regarding multiple induced abortions before a first live birth, we were unable to evaluate its effect on breast cancer risk due to the extremely low frequency in this population (<2% of women who had induced abortions). Nor were we able to adequately investigate the effect of induced abortion at a very young age. Future studies should assess these relations to clarify the role that induced abortion may play in breast cancer risk.

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Grant Abstract

Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer

Maureen Sanderson

Background: Endogenous estrogen, specifically estradiol, has been implicated as a causal factor for breast cancer. Critical periods of estrogen exposure are thought to be *in utero*, following menarche and around perimenopause. Factors associated with intrauterine estrogen exposure and prenatal growth, such as birth weight, have been related to breast cancer. Breast cancer associated with measures of postnatal growth, such as adolescent and adult weight and height, appears to differ by menopausal status. The different effect of weight and height on breast cancer by menopausal status may be explained, in part, by hormonal changes. Lower adult estrogen levels have been associated with low-fat, high-fiber diets. Insulin-like growth factor 1 (IGF1), which has been linked to breast cancer in several studies, may act in combination with estrogen. IGF1 concentrations are positively associated with height and body mass. Adults who were born at relatively low weights and who then become obese may have increased IGF1 and insulin levels. Decreased IGF1 concentrations have been associated with a low-calorie diet. Retinoids and vitamin D analogues also may lower IGF1 levels. Insulin resistance, like type 2 diabetes, is a condition characterized by high levels of insulin and by abdominal obesity. Excess weight gain and a high-fat, low-fiber diet may result in insulin resistance. Insulin resistance may place a woman at greater risk of developing breast cancer. The elevated risk of breast cancer among African-American (AA) women compared to European-American (EA) women may be related to their higher genetic susceptibility to insulin resistance.

Objective/Hypotheses: The purpose of this proposed Idea Award is to expand a newly funded Department of Defense (DOD) study of breast cancer to collect, process and analyze blood for estradiol (E2), sex hormone-binding globulin (SHBG), IGF1, insulin-like growth factor binding protein 3 (IGFBP3), insulin and glucose. The primary hypotheses are: 1) insulin resistance, defined as high levels of insulin and glucose or type 2 diabetes, will be positively associated with breast cancer, and 2) the insulin resistance-breast cancer association will be more pronounced among women with abdominal obesity, and elevated levels of E2 and IGF1. In addition, we will assess the role that birth weight, age at which adult height was achieved, diet, physical activity, and weight gain play in the insulin resistance-breast cancer relation.

Specific Aims: The specific aims of this proposed case-control study are: 1) to obtain information on type 2 diabetes, waist circumference, body mass index (BMI), birth weight, age at which adult height was achieved, diet, physical activity, and weight gain, and to collect pre-diagnostic blood, 2) to assay blood for E2, SHBG, IGF1, IGFBP3, insulin and glucose, and 3) to perform statistical analyses to assess the association between insulin resistance and breast cancer risk. The principal investigator received a Career Development Award (CDA) from DOD last year to study the interrelationships of prenatal and postnatal growth, hormones, diet and breast cancer. This proposed study would accomplish one aim of that CDA of obtaining funding to conduct a case-control study of the insulin resistance-breast cancer relationship.

Study Design: The case-control study onto which this proposed study will be grafted (i.e., the Parent Study) will consist of 648 incident breast cancer cases and 2592 controls who undergo diagnostic mammogram for breast cancer and are found later to be cancer free. Subjects will be recruited from two centers in South Carolina. The Parent Study is quasi-prospective in that women will be interviewed and biological samples will be collected prior to diagnosis. This

proposed study will recruit an additional 652 breast cancer cases, and will select 1300 women who receive a negative screening mammogram to form a separate, very low-risk control group. After completing a risk factor questionnaire, women will be asked to provide a fasting blood sample during their follow-up visit. The blood will be assayed for E2, SHBG, IGF1, IGFBP3, insulin and glucose.

Relevance: The interrelationships of prenatal and postnatal growth, hormones, diet, and breast cancer are complex. There is compelling evidence that insulin resistance may tie these relationships together, and may help explain the elevated risk of breast cancer among AA women. Should insulin resistance be associated with breast cancer, the possibility that genetic susceptibility and adolescent/adult diet and physical activity modifies this association will be useful in targeting interventions for women at high risk for breast cancer.

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Weight at birth and adolescence and premenopausal breast cancer risk in a low-risk population

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We assessed breast cancer risk in relation to weight at birth and adolescence. In-person interviews were completed with the biological mothers of women aged 45 years and younger who participated in the Shanghai Breast Cancer Study in 1996–98 (288 cases, 350 controls). After adjustment for confounding, women who were 4000 g or more at birth were not at increased risk of breast cancer (odds ratio=0.7; 95% confidence interval 0.4–1.4) relative to women whose birth weight was 2500–2999 g. Compared with women of average perceived weight at age 15 years, no relation was apparent for heavier than average weight based on maternal report (odds ratio=0.7; 95% confidence interval 0.5–1.2) or self-report (odds ratio=1.0; 95% confidence interval 0.7–1.6). Perceived adolescent weight and height did not modify the association of birth weight with breast cancer risk. These results suggest that weight early in life is not related to premenopausal breast cancer risk in this low-risk population.
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Keywords: breast cancer; birth weight; adolescent weight; adult body size

Epidemiology

Premenopausal breast cancer has been linked to high birth weight (Ekbom *et al*, 1992; Innes *et al*, 2000; Michels *et al*, 1996; Sanderson *et al*, 1996). Conversely, high adolescent (Coates *et al*, 1999; Hislop *et al*, 1986; Le Marchand *et al*, 1988a), early adult (Coates *et al*, 1999; Huang *et al*, 1997; Trentham-Dietz *et al*, 1997) and adult weight or body mass index (Brinton and Swanson, 1992; Huang *et al*, 1997; Swanson *et al*, 1996; Ursin *et al*, 1995; van den Brandt *et al*, 2000) appear to be protective against premenopausal breast cancer. Several studies have investigated the association between breast cancer and weight at birth (De Stavola *et al*, 2000; Ekbom *et al*, 1992, 1997; Innes *et al*, 2000; Le Marchand *et al*, 1988b; Michels *et al*, 1996; Sanderson *et al*, 1996, 1998a) or weight at adolescence (Brinton and Swanson, 1992; Choi *et al*, 1978; Coates *et al*, 1999; Franceschi *et al*, 1996; Hislop *et al*, 1986; Le Marchand *et al*, 1988a; Pryor *et al*, 1989) with inconsistent findings. Possible limitations of these studies related to exposure measurement and age at diagnosis of breast cancer.

Since self-report of body size in early life is prone to misclassification, maternal report may be less subjective. Maternal report was available for two of the studies investigating breast cancer risk associated with birth weight (Michels *et al*, 1996; Sanderson *et al*, 1998a), but none of the studies of adolescent weight. The present analysis was conducted to assess whether birth weight and adolescent weight as reported by subjects' mothers were related to premenopausal breast cancer risk. In addition, we investigated whether perceived adolescent weight and height modified the association of birth weight with breast cancer risk.

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MATERIALS AND METHODS

Detailed methods of this population-based case–control study appear elsewhere (Gao *et al*, 2000). Briefly, all women aged 25–64 years who were permanent residents of urban Shanghai at the time of diagnosis of first primary invasive breast cancer (August 1996 through March 1998) were eligible for the study. Two senior pathologists histologically confirmed all diagnoses. We used rapid case ascertainment supplemented by the Shanghai Cancer Registry to identify breast cancer cases who had no prior history of cancer. A total of 1459 breast cancer cases (91.1% of eligible cases) completed a standardized in-person interview. Of potentially eligible cases, 109 refused (6.8%), 17 died prior to the interview (1.1%), and 17 were not located (1.1%).

The Shanghai Resident Registry, a listing of all permanent adult residents of urban Shanghai, was used to randomly select controls. Controls were frequency matched to cases on age (5-year interval) based on the number of incident breast cancer cases by age group reported to the Shanghai Cancer Registry from 1990 through 1993. Women who did not reside at the registered address at the time of the study were ineligible. A total of 1556 controls (90.4% of eligible controls) completed a standardized in-person interview. The remaining 166 potentially eligible controls (9.6%) refused to participate. Two women died prior to the interview and were excluded.

The study was approved by relevant institutional review boards in Shanghai and the United States. Women were interviewed at hospitals (cases) or at home (cases and controls) by trained interviewers. The subject questionnaire collected information on demographic factors, reproductive and medical histories, family history of cancer, use of oral contraceptives and hormone replacement therapy, diet, physical activity, lifestyle factors, and adolescent and adult body size. Women were asked how their perceived weight and height compared with their peers at the ages of 10,

15 and 20. After completing the interview, women were weighed and had their standing and sitting height, and waist and hip circumferences measured. Information on exposures pertained to the period before an assigned reference date, the diagnosis date for breast cancer cases and a similar date for controls.

The biological mothers of women the age of 45 and younger who resided in Shanghai provided detailed information about the subject's adolescent diet and body size, and about her pregnancy with the subject. In-person interviews were completed with the mothers of 296 cases and 359 controls (with respective response rates of 79.6 and 81.8%). Eight cases and nine controls were subsequently excluded because they were postmenopausal, resulting in 288 cases and 350 controls for this analysis.

We used unconditional logistic regression to estimate the relative risk of breast cancer associated with weight at birth and adolescence while controlling for confounders (Breslow and Day, 1980). All variables were entered into models as dummy variables. In multiple logistic regression models, we assessed linear trend by treating categorical variables as continuous variables.

RESULTS

Table 1 compares known breast cancer risk factors of cases and controls. Compared to controls breast cancer cases were slightly older, had a lower income, and were more likely to have a history of fibroadenoma, a higher waist-to-hip ratio, and a later age at first birth. For consistency with most previous studies, subsequent analyses were adjusted for family history of breast cancer, menarcheal age, parity, and all of the preceding variables, except waist-to-hip ratio. Since adult waist-to-hip ratio may be in the causal pathway between birth and adolescent weight and breast cancer, it and adult body mass index were assessed as effect modifiers rather than as confounders. Further adjustment of birth weight for other perinatal factors did not materially change the odds ratios. Perceived weight is adjusted for perceived height at specific ages and vice versa.

Table 2 presents the odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer associated with maternal report of birth weight. After adjustment for confounding factors, women who were 4000 g or more at birth were not at increased risk of breast cancer (OR=0.7; 95% CI 0.4 – 1.4) relative to women whose birth weight was 2500 – 2999 g. When we dichotomized birth weight an identical odds ratio for women whose birth weight was 3500 g or more (OR=0.7, 95% CI 0.5 – 1.1) was found, compared with women who were less than 3500 g.

Table 2 Odds ratios of breast cancer associated with maternal report of birth weight

	Cases (*n*=288)	Controls (*n*=350)	OR[a]	(95% CI)
Birth weight (grams)				
<2500	14	18	0.9	(0.4 – 2.0)
2500 – 2999	58	70	1.0	(referrent)
3000 – 3499	122	135	1.1	(0.7 – 1.6)
3500 – 3999	35	53	0.8	(0.4 – 1.4)
⩾4000	18	29	0.7	(0.4 – 1.4)
P trend[b]			*P*=0.32	

[a]Adjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, and age at first live birth. [b]Excluding women less than 2500 g.

Table 1 Comparison of cases and controls for selected risk factors

	Cases[a] (*n*=288)	Controls[a] (*n*=350)	*P*-value
Age	39.6 ± 3.4	38.6 ± 3.9	<0.01
Education (%)			
Elementary education	1.0	0.0	
Middle+high school	91.7	90.9	
Profession, college and above	7.3	9.1	0.12
Per capita income (Yuan) (%)			
<4000	17.0	15.7	
4000 – 5999	48.6	37.7	
6000 – 7999	6.9	10.9	
8000 – 8999	14.6	24.6	
⩾9000	12.9	11.1	<0.01
Breast cancer in first degree relatives (%)	1.7	2.6	0.47
Ever had breast fibroadenoma (%)	11.5	5.4	<0.01
Regular alcohol drinker (%)	3.5	3.1	0.82
Ever used oral contraceptives (%)	6.6	7.4	0.68
Exercised regularly (%)	11.1	14.3	0.23
Body mass index	22.5 ± 3.1	22.3 ± 3.1	0.36
Waist-to-hip ratio	0.80 ± 0.06	0.78 ± 0.06	<0.01
Nulliparous (%)	6.6	5.1	0.43
Number of live births[b]	1.0 ± 0.19	1.0 ± 0.17	0.98
Age at first live birth[b] (years)	28.0 ± 3.3	27.5 ± 2.8	0.03
Months of breast feeding[c]	5.3 ± 4.9	5.4 ± 4.9	0.79
Menarcheal age (years)	14.3 ± 1.5	14.4 ± 1.6	0.45
Height (cm)	160.0 ± 5.1	159.9 ± 5.3	0.76
Weight (kg)	57.7 ± 8.8	56.9 ± 8.5	0.30

Subjects with missing values were excluded from the analysis. [a]Unless otherwise specified, mean ± s.d. are presented. [b]Among women who had live births. [c]Among women who ever breast fed.

Epidemiology

The risks for breast cancer associated with maternal and subject perceptions of subjects' weight and height at the age of 15 separately and combined are shown in Table 3. For mothers and subjects whose perceptions differed we created a fourth category. Compared with women of average perceived weight at the age of 15, no relation was apparent for heavier than average weight based on maternal report (OR=0.7; 95% CI 0.4–1.1) or self-report/combined maternal and subject report (OR=1.1; 95% CI 0.6–2.2). Elevated risks of breast cancer were seen for women whose mothers perceived they were shorter than average at age 15 (OR=2.1, 95% CI 1.3–3.5), which was reflected in the combined maternal and subject estimate (OR=1.9, 95% CI 1.0–3.7). We calculated Spearman correlation coefficients to assess the reliability of reporting of perceptions of weight and height by case–control status (Armstrong *et al*, 1992). The correlations comparing maternal and subject perceptions were reasonably consistent (weight r=0.46, height r=0.59).

Table 4 shows the joint effect of birth weight, adolescent weight, and adolescent height on breast cancer risk. The referent group is women who were less than 3500 g at birth, and who at the age of 15 were of average weight and average height. Perceived adolescent weight and height did not modify the effect of birth weight on breast cancer risk or vice versa. Women whose birth weight was 3500 g or more and who perceived themselves to be of low or average adolescent weight and low or average adolescent height were at reduced risk of breast cancer (OR=0.4, 95% CI 0.2–0.8). Neither adult body mass index nor waist-to-hip ratio modified the effect of birth weight or adolescent weight on breast cancer risk (data not shown).

DISCUSSION

We found no association between high birth weight and premenopausal breast cancer, in agreement with some (De Stavola *et al*, 2000; Ekbom *et al*, 1997; Le Marchand *et al*, 1988b; Sanderson *et al*, 1998a), but not all (Ekbom *et al*, 1992; Innes *et al*, 2000; Michels *et al*, 1996; Sanderson *et al*, 1996), of the previous studies of this topic. Trichopoulos (1990) hypothesized that exposure to high levels of endogenous estrogen *in utero* may be a possible risk factor for subsequent breast cancer. In a study conducted in Greece, high birth weight was associated with high pregnancy estrogen levels (Petridou *et al*, 1990). However, Lipworth *et al*. (1999) reported substantially higher mean levels of pregnancy estrogens and significantly lower mean birth weights among women in Shanghai than among their counterparts in Boston. They speculated that higher albumin and sex hormone binding globulin among Chinese women could decrease the bioavailability of oestrogens. This may partially explain the lack of a positive association with high birth weight observed in the present analysis.

The results of studies on adolescent weight and premenopausal breast cancer risk are inconsistent. Premenopausal breast cancer risk associated with heavier than average weight at the age of 15 or thereabouts was decreased in some studies (Coates *et al*, 1999; Hislop *et al*, 1986; Le Marchand *et al*, 1988a), increased in one study (Pryor *et al*, 1989), and had no association in other studies (Brinton and Swanson, 1992; Choi *et al*, 1978; Franceschi *et al*, 1996). The reduction in risk reported by Le Marchand *et al*. (1988a) was for the highest tertile of body mass index compared with the lowest tertile (OR=0.45, 95% CI 0.23–0.86). This relation

Table 3 Odds ratios of breast cancer associated with perceptions of adolescent body size

	Cases (n=288)	Controls (n=350)	OR[a]	(95% CI)
		Maternal perceptions		
Perceived weight at age 15 years[b]				
<Average	67	75	1.2	(0.8–1.7)
Average	186	219	1.0	(Referent)
>Average	34	56	0.7	(0.4–1.1)
Perceived height at age 15 years[c]				
<Average	46	34	2.1	(1.3–3.5)
Average	164	236	1.0	(Referent)
>Average	77	80	1.4	(0.9–2.0)
		Subject perceptions		
Perceived weight at age 15 years[b]				
<Average	101	132	1.0	(0.7–1.4)
Average	144	169	1.0	(Referent)
>Average	42	49	1.1	(0.7–1.7)
Perceived height at age 15 years[c]				
<Average	47	61	1.1	(0.7–1.7)
Average	156	194	1.0	(Referent)
>Average	85	95	1.2	(0.8–1.7)
		Maternal and subject perceptions combined		
Perceived weight at age 15 years[b]				
<Average	51	55	1.1	(0.7–1.8)
Average	118	128	1.0	(Referent)
>Average	20	22	1.1	(0.6–2.2)
Did not agree	98	145	0.8	(0.5–1.1)
Perceived height at age 15 years[c]				
<Average	25	21	1.9	(1.0–3.7)
Average	120	161	1.0	(Referent)
>Average	58	58	1.4	(0.9–2.2)
Did not agree	85	110	0.9	(0.7–1.5)

[a]Adjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, and age at first live birth. [b]Additionally adjusted for perceived height at specific age. [c]Additionally adjusted for perceived weight at specific age.

Table 4 Odds ratios of breast cancer associated with joint effects of birth weight, adolescent weight and adolescent height

		Birth weight					
		<3500 g			⩾3500 g		
		Case/Ctrl	OR[a]	(95% CI)	Case/Ctrl	OR[a]	(95% CI)
Maternal perceptions							
Weight at 15 years	Height at 15 years						
⩽Average	⩽Average	141/150	1.0	(Referrent)	28/45	0.7	(0.4–1.1)
	>Average	32/38	0.8	(0.5–1.4)	18/21	1.0	(0.5–1.9)
>Average	⩽Average	14/27	0.6	(0.3–1.1)	3/9	0.3	(0.1–1.2)
	>Average	7/8	0.9	(0.3–2.5)	4/7	0.6	(0.2–2.1)
Subject perceptions							
Weight at 15 years	Height at 15 years						
⩽Average	⩽Average	136/148	1.0	(Referrent)	20/46	0.4	(0.2–0.8)
	>Average	37/48	0.8	(0.5–1.3)	21/24	1.0	(0.5–1.9)
>Average	⩽Average	13/17	0.9	(0.4–2.0)	6/8	0.8	(0.3–2.3)
	>Average	8/10	0.8	(0.3–2.1)	5/4	1.6	(0.4–6.7)

[a]Adjusted for age, income, family history breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, and age at first live birth.

was more pronounced among women who were heavier than average during adolescence and whose adult body mass index was at or above the median (OR=0.31, 95% CI 0.16–0.60). In the present analysis, no relation was apparent for breast cancer associated with heavier than average perceived weight at the age of 15 based on maternal report or self-report. Neither adult body mass index nor waist-to-hip ratio modified the effect of perceived adolescent weight on breast cancer risk.

The biological mechanism that Stoll (1998) proposed to help explain the reduced risk of premenopausal breast cancer associated with adolescent obesity in some studies was that obesity triggered a hyperinsulinemic insulin resistance at puberty that could lead to abnormal ovarian steroidogenesis and anovulation. Most of the women in this study grew up during a period when food and meat were rationed and adolescent obesity was rare, thus perceived weight at the age of 15 may not reflect adolescent obesity as defined among Western women. Spearman correlation coefficients were calculated to assess whether age at menarche, used as a marker of adolescence, was correlated with perceived weight or height at the age of 15. Whether reported by the subject or her mother, these correlations were negative and clustered around zero.

In a previous analysis of this study, premenopausal breast cancer was unrelated to early adult and adult weight, but was associated with a high adult waist-to-hip ratio, even after adjustment for body mass index (Shu *et al*, 2001). These findings differ from the majority of studies of this topic conducted among Western women. As was the case for early adult and adult weight, an alternative explanation for the null associations found for weight at birth and adolescence and breast cancer risk is the paucity of women at the extremes of these measures.

Our findings of increased risks of premenopausal breast cancer associated with maternal report and combined maternal and subject report of perceived height as shorter than average at the age of 15 differs from all previous studies. Coates *et al*. (1999) reported reduced risks for women who were much shorter than average at the ages of 15 to 16. Brinton and Swanson (1992) reported an increased premenopausal breast cancer risk associated with taller than average perceived height at the age of 16. An earlier adolescent growth spurt and tallness in childhood has been linked to earlier menarche (Preece, 1989), an established breast cancer risk factor. In the present study, the mean menarcheal age was approximately 14.5 years, which was nearly 2 years later than the mean age among US women at the time the majority of women in this study were achieving menarche (Zacharias *et al*, 1976). The later age at menarche experienced by women in China meant that some of the women in the present analysis had not undergone their adolescent growth spurt by the age of 15, which may partially explain the lack of a positive association observed in this study with taller adolescent height.

One previous study has investigated the joint effect of birth weight and adolescent weight or adolescent height on breast cancer risk. De Stavola *et al*. (2000) recently examined the effects of birth weight and childhood growth on subsequent breast cancer risk in a cohort study in the UK. They reported a borderline increase in risk of premenopausal breast cancer associated with a birth weight of 3500 g or more (relative risk [RR]=2.31, 95% CI 0.93–5.74). This risk was modified by height at the age of 7, with no association among women who were short or average (RR=1.23, 95% CI 0.31–4.91) and a pronounced elevation in risk among women who were tall (RR=5.86, 95% CI 1.97–17.44). They concluded that the birth weight and breast cancer relation might be mediated through childhood growth. Height at the age of 7 was chosen to reflect pre-pubertal growth, but there was no significant interaction for the height at the age of 15. In the present analysis, perceived height at the age of 10 (data not shown) and the age of 15 did not modify the effect of birth weight on breast cancer risk. However, women who were 3500 g or more and short or average height at the age of 15 were at decreased risk of breast cancer.

There were several limitations of this study. Data on birth weight and maternal perception of adolescent body size analyses were available only in a subgroup of premenopausal women, reducing statistical power to detect effect modification. The narrow distribution of weights at birth and adolescence in China (Eveleth and Tanner, 1976; Fung *et al*, 1989) may have further limited the statistical power to evaluate the association of these variables with breast cancer risk. Reporting of birth weight and perceptions of weight and height during adolescence are prone to misclassification. However, in a study conducted in Washington State, we found very high correlations between maternal reporting and birth certificate recording of birth weight (case mothers r=0.89, control mothers r=0.84) (Sanderson *et al*, 1998b). To our knowledge, no validation studies of maternal reporting of adolescent body size have been conducted.

This study has many strengths. The population-based nature of the study and its high response rates among subjects (cases: 91%; controls: 90%) and their mothers (case mothers: 80%; control mothers: 82%) minimizes selection bias. We adjusted for known breast cancer risk factors, and evaluated the weight at birth and adolescence and breast cancer associations in conjunction with

suspected effect modifiers of these relations. An additional strength of the study was the good agreement between maternal and subject reporting of adolescent body size. There are, however, some measurement errors, which may have attenuated the estimated odds ratios is this study.

In summary, our study indicates that weight at birth and adolescence has little influence on breast cancer risk in Chinese women. These results suggest that weight early in life is not related to premenopausal breast cancer risk in this low-risk population. Future studies should assess these relations to clarify the role that weight early in life may play in breast cancer risk.

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Dietary exposures and oral precancerous lesions in Srikakulam District, Andhra Pradesh, India

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Abstract

Objective: To test the effect of dietary nutrients on oral precancerous lesions in a reverse-smoking (i.e. smoking with the glowing end inside the mouth) population in South India.

Design: Case–control. Cases with precancerous lesions were matched to an equal number of lesion-free controls matched on age (±5 years), sex and village. All subjects used tobacco in some form. Dietary data were obtained using an interviewer-administered food-frequency questionnaire, designed for use in this population. All interviews were conducted blinded to the disease status of the subject. Data were analysed using logistic regression.

Setting: Nineteen rural villages in Srikakulam District, Andhra Pradesh.

Subjects: From a survey of 6007 tobacco users, 485 (79% women) were found to have precancerous, mostly palatal, lesions (cases), and 487 lesion-free subjects were selected as controls.

Results: All eligible subjects consented to participate and nearly all (>99%) had complete data for analyses. Reverse smoking was the most common form of tobacco use among cases (81.9%) and controls (73.5%), and reverse smokers were 5.19 times more likely than chewers to have these lesions (95% confidence interval = 1.35, 19.9). After controlling for relevant covariates, including the type of tobacco use, protective linear effects were observed for zinc (70% reduction across the interquartile range, $P < 0.002$), calcium (34% reduction, $P < 0.002$), fibre (30% reduction, $P < 0.009$), riboflavin (22% reduction, $P < 0.03$) and iron (17% reduction, $P < 0.05$).

Conclusions: Several dietary nutrients appear to protect against oral precancerous lesions that are strongly associated with reverse smoking. The results of this study indicate scope for targeting dietary factors in preventing oral cancer, which should be coupled with aggressive anti-tobacco use efforts.

Keywords
India
Oral neoplasms
Precancerous conditions
Dietary nutrients

Oral cancer is the sixth commonest cancer in the world[1]. Its incidence is particularly high in India, some other countries in Asia, and in certain places in the Western hemisphere, e.g. parts of France and Brazil, where smoking and alcohol drinking are major risk factors. In India, chewing and smoking of tobacco products in various forms is primarily responsible for the high incidence. The World Health Organization (WHO) has estimated that 90% of oral cancers in India among men were attributable to chewing and smoking habits[2]. In previous work, it has been shown that reverse smoking (i.e. with the glowing end inside the mouth), a practice common among women in a coastal region of Andhra Pradesh in east–central India, is strongly associated with oral, particularly palatal, precancerous lesions that may progress to carcinoma and may exhibit epithelial atypia of the palate[3–5].

Nutritional risk factors also have been implicated in cancers of the oral cavity. A number of studies have indicated that the consumption of various vegetables and fruits reduces risk. These relationships may be independent of other risk factors and show a dose–response effect[6–10]. However, any cancer of the alimentary tract can

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affect dietary intake, which in turn may affect the accuracy of assessment of usual dietary habits among cases[11].

Within the oral cavity, cancer generally develops on the tongue, buccal mucosa, gingiva, lips, floor of the mouth, but less often on the palate, except in reverse smokers among whom it is the most common location. In the region of this study, Srikakulam District, Andhra Pradesh, reverse smoking is practised using *chutta*, a coarsely made cheroot (cigar with both ends open) about 5–12 cm long[5]. The prevalence and incidence of these precancerous palatal and other mucosal changes are very high among such reverse smokers[12].

Oral, including palatal, cancer often is preceded by precancerous lesions[13]. The relative risk of developing oral cancer among individuals with oral precancerous lesions has been found to be very high (i.e. >200), demonstrating the fact that such lesions lie on the causal pathway to cancer[14]. The association of oral precancerous lesions with tobacco habits follows a pattern similar to that of oral cancer[12]. Because the prevalence of oral precancerous lesions is much higher than that of oral cancer, these conditions provide a useful clinical marker for oral cancer. For this reason, they have been used as such in large-scale intervention trials[15]. In addition to improving the outcome yield of such studies, using precancerous lesions provides an opportunity to avoid some of the biases associated with measuring dietary intake in individuals with oral cancer. Clearly, the high rate of oral cancer underlines this as a matter of great public concern and the presence of a precancerous marker lesion makes careful epidemiological study more feasible. A probable wide range of variability in nutrient exposures[16–18] that could overcome a common problem with limitations in the distribution of nutrient intake[19] provided an additional rationale for evaluating dietary factors for oral cancer precursors in India.

The primary goal of this research was to test the relationship between the presence of precancerous changes in the mouth and the dietary intake of: the antioxidants, β-carotene and ascorbic acid; the B vitamins, thiamine and riboflavin; and the trace elements, iron, copper, calcium and zinc. These micronutrients were chosen on the basis of a variety of laboratory studies[20,21], human experimental studies[22–26], observational studies[27–30] and the availability of data in the nutrient database[31].

Methods

Subject recruitment/data collection

This population-based case–control study was conducted in 19 villages not included in earlier studies in Srikakulam District, Andhra Pradesh[12,32]. A preliminary census was conducted for listing households along with the identification information for each member of the household and their tobacco use status.

A team consisting of dentists, field investigators and a social scientist especially trained in conducting diet–nutrition interviews visited each household on the house lists with the aim of examining all tobacco users aged 15 years and over. As the first step in the recruitment/data collection process, a field investigator interviewed the potential study subject and filled out a questionnaire containing basic demographic information and details of tobacco and alcohol habits. An experienced dentist then examined the subject for the presence of oral precancerous lesions. The subject was then classified as a case if she or he had an eligible precancerous lesion (palatal changes consisting of patches and red areas, leukoplakia, erythroplakia, submucous fibrosis, and an ulcer or a growth suspicious of oral cancer). In the initial survey, 6007 tobacco users were examined. Of these, 485 were found to have one or more lesions necessary to qualify them as a case. The potential control pool consisted of all examined persons who were found to be free of lesions. A control ($n = 487$) was identified as the next available examinee found to be free of lesions, and matched on sex, age (±5 years) and village. Because of the design of the study all cases and controls used tobacco in some form. Therefore, type of tobacco habit (yes/no for each category, chewing, smoking, reverse smoking) was recorded and used as a control variable in all statistical analyses. All selected cases and controls consented to participate in the study.

An 80-item food-frequency questionnaire (FFQ) specific to this population was developed with an aim of estimating nutrient intake. This was similar to instruments developed for use in Kerala[33] and Gujarat[34]. The FFQ interview for the case–control study was conducted only if a subject was selected to participate and after obtaining informed consent. To minimise the likelihood of bias, all data were collected in a blinded fashion (i.e. the interviewer was not aware of the status of the subject and the subject was not told of the presence or absence of the lesion until completion of the interview, within 5 days of the exam). Therefore, unlike in most case–control studies, the FFQ was administered without anyone involved in the collection of the dietary data having knowledge of the subject's disease status.

The FFQ took approximately 25 minutes to complete. It consisted of questions on the typical frequency and quantity of consumption of 80 food items representing >95% of exposure to total energy, fat, fibre, iron, copper, zinc, calcium, ascorbic acid, β-carotene and the B vitamins in this population.

FFQ validation

The FFQ specifically developed for use in this population was validated for collecting dietary information and estimating nutrient intake. The nutrient database[31] was the same as used in previous work by our group[33,34]. Some 60 people (30 male/female pairs) living in the broad area

of this study, but not in the villages sampled for the case–control study, were selected for the validation study (i.e. it was an external validation study). On eight randomly selected days over the year, subjects were administered 24-hour diet recall interviews (24HR). The FFQ was administered twice, exactly a year apart. A brief description of the results of the comparison between the FFQ- and 24HR-derived nutrient values is included in this paper.

Oral precancerous lesions

Palatal changes constitute the most important precancerous changes among reverse *chutta* smokers, the most common form of tobacco use in this region. Two components of these palatal changes, namely patches and red areas, were included in this study. Patches were defined as well-demarcated, slightly elevated plaques, which qualify for the clinical term leukoplakia[4]. Red area was defined as palatal mucosa showing well-defined reddening without ulceration[4]. Other non-palatal lesions included in this study were leukoplakia classified into homogeneous, nodular and ulcerated (for a detailed description see Pindborg[13]) and oral submucous fibrosis. In two females, lesions suspicious of being oral cancer were confirmed as such on histopathological examination and referred for care. It is important to note that both heat from reverse smoking and products of tobacco combustion play important roles in carcinogenesis, although it is not feasible to delineate the effect of each[12,15].

Tobacco habits

Reverse *chutta* smoking was the common form of smoking in this region[5], especially among women; 98% of women tobacco users engaged in this practice. In this study, overall, a minority of individuals smoked *bidis* (2.6%), cigarettes (1.7%) and *chutta* in the conventional manner (14.3%), or chewed tobacco (2.2%). *Chutta* is a coarsely prepared cheroot. *Bidi* is a smoking stick prepared by rolling 0.15–0.25 g of sun-dried flake-form of tobacco in a rectangular dried piece of *temburni* leaf (*Diospyrous melanoxylon*). Details of these and other forms of tobacco habits in India are described elsewhere[35].

Statistical methods

For the external validation study, nutrient scores derived from the FFQ were compared with those derived from the eight 24HR administered on randomly selected days over the one-year study period. Pearson product moment and Spearman rank order correlations were used as the criteria for comparison.

Descriptive statistics were computed overall and separately for cases and controls. These consisted of either standard parametric statistics for continuous variables (e.g. the nutrient scores) or non-parametric frequency statistics for all variables measured on an ordinal or nominal scale or as counts. The 25th, 50th and 75th percentile values for each of the nutrient scores were computed based on the entire dataset. Multivariable analysis was conducted using logistic regression. Because of the strength of association between specific types of tobacco use and oral cancer and precancer, some designation of tobacco habit was considered in specifying all statistical models. Two indicator variables describing the three major categories of tobacco use in this population (reverse *chutta* smoking, smoking in the conventional manner and chewing tobacco in any form (referent group)) was conceptually the simplest scheme and had the largest explanatory ability of any alternative. Duration of use was closely associated with age and no measure of intensity appeared to affect estimates of risk after accounting for type of tobacco use.

Social and economic variables often serve as proxies for potentially important risk factors for cancer and therefore are frequently included in analyses. As the vast majority (93%) of the population was illiterate, it was not possible to use education, one of our two indicators, in analyses. For reasons of multicollinearity, it also was not possible to include economic status (described as either higher – a brick house with tiled or corrugated tin roof; or lower – a mud house with thatched roof) because it was strongly related to smoking; e.g. for overall smoking (including reverse smoking) the Mantel Haenzel chi-square was 4.24 ($P = 0.04$), whereas for conventional smoking the chi-square was 52.36 ($P < 0.0001$). Nutrient scores were included both as continuous variables and quartiles, in separate models, because dietary nutrients are highly correlated with one another. Because dietary exposure estimates may be biased by overall errors in reporting[36,37] and some nutrients have a stoichiometric relation with total energy utilisation[38], we controlled for total energy intake by fitting it as a covariant in each model. For nutrients evincing linear effects, we computed the effect across the interquartile range of its distribution, thus standardising the effect for the distributions of nutrient exposure reported in this population.

The primary analyses were conducted on the main study data for all types of lesions combined. Additional analyses were conducted by gender and by lesion type. All analyses were conducted using the personal computer version of SAS[39,40].

Follow-up study

After one year, all 6007 tobacco users were re-examined. Among those found to be lesion-free at the first survey, 39 had a new incident lesion. For each case thus identified, a control was selected. These data were analysed separately in the same manner as for the main case–control study dataset. In order to assess whether the expected wide confidence interval (CI) was simply due to sample size (and not other factors affecting precision), we adjusted the 95% CI for the ratio of the sample sizes of the prevalent and incident case series. The 'sample-size-adjusted' 95% CI

is obtained by the formula antilog $[b \pm 1.96\mathrm{SE}_b/\sqrt{n_\mathrm{p}/n_\mathrm{i}}]$, where b = log odds ratio, SE_b = standard error of b, n_p = number of prevalent cases and n_i = number of incident cases.

Results

Table 1 shows the results from the external validation study. These consist of correlation coefficients for each of the nutrients of interest plus total energy intake, a control variable fit in all logistic regression models. Correlation coefficients for total fat and fat as percentage of energy also are shown. With the exception of sodium, ascorbic acid and β-carotene, the correlation coefficients were moderately high, comparing very favourably with those of other studies[41].

The descriptive statistics of the study population, including the reported daily nutrient intakes as estimated by the FFQ, are shown in Table 2. In both the validation study and the case–control study, there was an apparent miscalibration for rice preparations (rice, rice with starch water, and rice with buttermilk). These preparations represented 78% of total caloric intake reported in this population; about three times higher than expected based on estimates from other rice-eating populations[16] including a group we had studied in Kerala[33]. As presented, energy intake represents the total from the remaining 77 foods, but with a re-calibration of rice intake based on measurements from the predominantly rice-eating study population in Kerala[33]. This was done by computing the metabolic need per kg body weight by sex in Kerala (i.e. kcal kg^{-1} day^{-1}) and applying that rate to an individual's consumption of rice in *this* population. In all analyses of study data, the intake of energy actually reported (and not the adjusted value shown in the table) was used as a control variable. This was done to avoid using imputed data in the regression analyses.

Due to miscalibration of rice intake, the intake of many nutrients was overestimated because of the amounts involved (even though rice normally is only a minor

Table 1 Results of correlation analyses – Food-Frequency Questionnaire External Validation Study, Srikakulam District, Andhra Pradesh, India, 1993–94*

	Pearson product moment correlation†		Spearman rank correlation‡	
Nutritional variable	Pre	Post	Pre	Post
Total energy (kcal day^{-1})	0.55	0.55	0.64	0.50
Total fat (g day^{-1})	0.68	0.67	0.65	0.56
Fat (% energy)	0.81	0.81	0.72	0.70
Fibre (g day^{-1})	0.70	0.62	0.71	0.53
Iron (mg day^{-1})	0.44	0.38	0.53	0.33
Sodium (mg day^{-1})	0.29	0.14	0.34	0.31
Copper (mg day^{-1})	0.62	0.48	0.61	0.36
Zinc (mg day^{-1})	0.62	0.69	0.69	0.65
Calcium (mg day^{-1})	0.56	0.32	0.65	0.37
Ascorbic acid (mg day^{-1})	0.08	0.30	−0.005	0.31
β-Carotene (μg day^{-1})	0.10	0.15	0.18	0.26
Thiamine (mg day^{-1})	0.61	0.57	0.65	0.43
Riboflavin (mg day^{-1})	0.55	0.51	0.60	0.45

* In all instances $P < 0.05$ if $|r| > 0.25$, total $n = 60$.
† This is the parametric coefficient obtained in correlating the FFQ-derived nutrient score with the equivalent 24HR-derived nutrient score.
‡ This is based on the rank order (non-parametric) correlation.

Table 2 Descriptive statistics – Diet and Oral Precancer Study, Srikakulam District, Andhra Pradesh, India, 1993–95*

	Cases		Controls	
Categorical variable*	*n*	(%)	*n*	(%)
Males	104	(21.4)	108	(22.2)
Females	381	(78.6)	379	(77.8)
Occupation				
Business/Professionals	3	(0.6)	2	(0.4)
Farming/Merchandise	25	(5.2)	39	(8.0)
Skilled labour	32	(6.6)	17	(3.5)
Secretarial/Clerical	9	(1.9)	8	(1.6)
Unskilled/Self-employed	229	(47.2)	257	(52.8)
Householder	187	(38.6)	164	(33.7)
Education				
Illiterate	451	(93.0)	451	(92.6)
Primary	21	(4.3)	24	(4.9)
Middle	12	(2.5)	6	(1.2)
High school	1	(0.2)	3	(0.6)
College	0	–	3	(0.6)
Social category				
Forward	206	(42.5)	222	(45.6)
Backward	196	(40.4)	171	(35.1)
Schedule	83	(17.1)	94	(19.3)
Socio-economic status				
Low	442	(91.1)	457	(93.8)
Medium	43	(8.9)	30	(6.2)
Tobacco use				
Chewing	3	(0.6)	18	(3.7)
Smoking	56	(11.5)	72	(14.8)
Smoking and chewing	29	(6.0)	39	(8.0)
Reverse smoking	397	(81.9)	358	(73.5)
Continuous variable†	Mean	(SD)	Mean	(SD)
Age (years)	52.1	(10.4)	51.3	(10.4)
Nutrients†‡				
Total energy (kcal day^{-1})§	1981	(408)	1998	(404)
Total fat (g day^{-1})	33.4	(22.4)	33.4	(14.2)
Fat (% energy)	15.4	(9.8)	15.2	(6.0)
Fibre (g day^{-1})	12.3	(5.0)	13.3	(5.9)
Iron (mg day^{-1})	23.3	(8.2)	24.5	(8.8)
Sodium (mg day^{-1})	83.2	(62.1)	88.7	(51.5)
Copper (mg day^{-1})	2.05	(0.70)	2.15	(0.82)
Zinc (mg day^{-1})	18.3	(5.5)	18.9	(6.1)
Calcium (mg day^{-1})	939	(452)	1046	(495.4)
Ascorbic acid (mg day^{-1})¶	4.3	(0.4)	4.3	(0.4)
β-Carotene (μg day^{-1})¶	7.4	(0.6)	7.5	(0.5)
Thiamine (mg day^{-1})	1.51	(0.56)	1.62	(0.64)
Riboflavin (mg day^{-1})	1.33	(0.38)	1.38	(0.40)

* Values presented are the number and percentages of all cases and controls with the attribute.
† Value is the mean and standard deviation (SD) by case and control status.
‡ Nutrients are daily amounts as calculated from the food-frequency questionnaire, as described in the text.
§ Energy intake is adjusted to account for overreporting of rice intake, as reported in the text.
¶ Values of these nutrients are log-transformed to normalise the distribution.

Table 3 Distribution of lesion types – Diet and Oral Precancer Study, Srikakulam District, Andhra Pradesh, India, 1993–95*

	Male		Female	
	n	(%)	*n*	(%)
Palatal changes (patches)	54	(51.9)	332	(87.1)
Palatal changes (red areas)	5	(4.8)	43	(11.3)
Leukoplakia	46	(44.2)	14	(3.7)
Submucous fibrosis	2	(1.9)	–	–
Carcinoma	–	–	2	(0.5)
Total number of subjects with qualifying lesions	104		381	

*Tabulated values are the number of subjects (cases) with each lesion. The value in parentheses is the proportion of males or females having the lesion. Because of multiple lesions, the total will add to a number greater than 100%.

contributor to intake of most of these nutrients). Exceptions were ascorbic acid and β-carotene, to which the contribution of rice is nil. It must be emphasised that the miscalibration in reporting rice intake appeared to be uniform across the whole study and it affected the intake values only through change of origin and scale. Correlation, however, is not affected by any change in origin or scale, and for most nutrients the correlation coefficients were relatively high, as they were for total energy (Table 1).

The distribution of lesions among the 485 cases is presented in Table 3. Among women, almost all lesions were located on the palate; whereas among men, slightly over half of all lesions were located on the palate. Smoking, in any form, was associated with elevated risk. Odds ratios (ORs) for smoking were consistent, irrespective of what control variables were fit in the model. In the model with no dietary or economic variables included, relative to chewing only, the OR for reverse *chutta* was 5.19 (95% confidence interval (CI)=1.35, 19.9) and for conventional smoking it was 3.63 (95% CI = 0.96, 13.74). As with results based on analyses of other data from these same study areas, alcohol intake was minimally associated with the presence of these lesions[42]. Inclusion of any other predictor, including alcohol, did not materially affect the size or significance of these relationships. When restricting the analysis to females, information on tobacco habit was omitted from the model because virtually all (98%) women tobacco users were reverse *chutta* smokers.

Table 4 presents the OR and 95% CI for each of the eight nutrients found to be related to oral precancerous lesions. Six were found to have linear protective effects and two were found to be associated with reduced risk at any level above the lowest quartile of intake. For those linearly related, we show the effect of the nutrient across the interquartile range of its distribution as a way of standardising their effects. In all models, virtually identical results were observed for all control variables. For all six nutrients fit as continuous variables, the model had higher overall explanatory ability than did the quartile alternative.

Models not shown analogous to those in Table 4 but fit for women separately showed very similar results, owing to the preponderance of women in this study. Among men, except for zinc (OR = 0.87, or a 13% reduction in risk per gram of zinc consumed per day, $P = 0.06$), the results did not approach statistical significance. However, the point estimates of the ORs were similar for men and women.

Table 4 Adjusted odds ratios for nutrients in relation to overall lesions – Diet and Oral Precancer Study, Srikakulam District, Andhra Pradesh, India, 1993–95*

	OR (95% CI)	*P*-value	Effect across interquartile range (%)†
Nutrients best fit as a continuous variable‡			
Iron (10 mg day^{-1})	0.82 (0.68, 0.99)	0.04	(16.6)
Zinc (mg day^{-1})	0.91 (0.85, 0.98)	0.02	(70.2)
Copper (mg day^{-1})	0.83 (0.67, 1.03)	0.09	(16.0)
Calcium (100 mg day^{-1})	0.95 (0.92, 0.98)	0.001	(33.6)
Riboflavin (mg day^{-1})	0.51 (0.28, 0.93)	0.03	(22.1)
Fibre (g day^{-1})	0.96 (0.94, 0.99)	0.007	(29.6)
Nutrients exerting non-linear effects§			
β-Carotene (highest 3 quartiles)	0.78 (0.58, 1.05)	>0.10	
Ascorbic acid (highest 3 quartiles, females only)	0.82 (0.59, 1.13)	>0.10	

*Nutrients shown are ones hypothesised to be related to risk of oral cancer or precancer. Odds ratios (ORs) and their 95% confidence intervals (CIs) are based on seven separate logistic regression models, one for each of the seven nutrients shown (excluding ascorbic acid). Each model controlled for type of tobacco habit and total energy consumption (kcal day^{-1}). For ascorbic acid, type of tobacco habit was omitted because virtually all women were reverse *chutta* smokers.

† For each nutrient fit as a continuous variable, the effect was standardised by computing the difference of effect at the 75th percentile value (OR×nutrient$_{75}$) and its effect at the 25th percentile value (OR×nutrient$_{25}$). The value shown represents the percentage reduction across the interquartile range. The respective 25th, 50th and 75th percentile values for each nutrient shown are as follows: iron (mg day^{-1}) – 18.5, 23.1 and 27.7; zinc (mg day^{-1}) – 14.7, 19.4 and 22.5; copper (mg day^{-1}) – 1.55, 2.04 and 2.49; calcium (mg day^{-1}) – 583, 974 and 1255; riboflavin (mg day^{-1}) – 1.11, 1.36 and 1.56; fibre (g day^{-1}) – 8.5, 12.1 and 15.9; β-carotene (μg day^{-1}) – 1180, 1675 and 2405; ascorbic acid (mg day^{-1}) – 57.2, 74.4 and 93.7.

‡ Each nutritional variable is fit as a continuous variable. The units are modified to permit easier interpretation of the odds ratio (e.g. the OR shown for calcium represents the fraction of risk with each 100 mg consumed per day).

§ These variables were found to have an effect, which was clearly non-linear. In each instance the referent is the lowest quartile of reported intake.

Table 5 Adjusted odds ratios for nutrients in relation to overall newly incident lesions – Diet and Oral Precancer Study, Srikakulam District, Andhra Pradesh, India, 1993–95*

	OR (95% CI)	Sample-size-adjusted 95% CI†
Nutrients best fit as a continuous variable†		
Iron (10 mg day^{-1})	0.82 (0.39, 1.69)	(0.67, 1.00)
Zinc (mg day^{-1})	0.88 (0.63, 1.22)	(0.80, 0.96)
Copper (mg day^{-1})	0.77 (0.35, 1.73)	(0.61, 0.97)
Calcium (100 mg day^{-1})	0.98 (0.87, 1.10)	(0.95, 1.01)
Riboflavin (mg day^{-1})	0.39 (0.03, 4.53)	(0.20, 0.77)
Fibre (g day^{-1})	0.97 (0.88, 1.06)	(0.94, 1.00)

* Nutrients shown are ones hypothesised to be related to risk of oral cancer or precancer. Odds ratios (ORs) and their 95% confidence interval (CIs) are based on six separate logistic regression models, one for each of the nutrients shown. Each model controlled for type of tobacco habit and total energy consumption (kcal day^{-1}).
† This is the 95% confidence interval adjusted for the sample size observed in the main study (based on 485 eligible lesions).

Analyses based on palatal changes consisting of patches were similar to those based on overall lesions, with significant protective effects for calcium (OR = 0.95; 95% CI = 0.92, 0.98), riboflavin (OR = 0.46; 95% CI = 0.23, 0.93) and fibre (OR = 0.97; 95% CI = 0.94, 0.99). Point estimates of the OR in women and in men were virtually identical (though none were statistically significant in men). Results from analyses of palatal changes consisting of red areas showed a protective effect of zinc in the higher quartiles of intake: for quartile 2, OR = 0.11 (95% CI = 0.02, 0.57); for quartile 3, OR = 0.09 (95% CI = 0.01, 0.74); and for quartile 4, OR = 0.05 (95% CI = 0.003, 0.80). Results in women were identical to the overall results. There also was a larger decrease in risk from calcium (OR = 0.92, 95% CI = 0.82, 0.99) for red areas, as compared with patches. Leukoplakia-specific results were unremarkable, with only suggestions of protective effects in women for zinc (OR = 0.38; 95% CI = 0.14, 1.08), fibre (OR = 0.80; 95% CI = 0.61, 1.05) and calcium (OR = 0.73; 95% CI = 0.52, 1.02).

Analyses focusing on newly incident cases (Table 5) were meant to corroborate the results of the main case–control study shown in Table 4. Due to the small sample size and the confirmatory nature of that portion of the study, there was neither an intention of formal hypothesis testing nor one of examining effects in any subset of the data. Among individuals who were originally lesion-free, 39 were found to have one or more lesions after one year (cases). One such person was included as a control in the main case–control study, but was classified as a case in this follow-up dataset. All female cases were reverse *chutta* smokers. Of the 32 women with lesions, 30 had palatal patches and two had red areas. Among seven new male incident cases, five were diagnosed with leukoplakia, one had palatal changes, and one had lichenplanus. Despite very wide confidence limits, as expected, the point estimates of the ORs were similar to those presented in Table 4. When we 'adjusted' the 95% CI to the size of sample in the main study, they were very similar to those shown in Table 4.

Discussion

Studies attempting to relate diet with oral cancer must confront two major obstacles, one inherent in the relationships among relevant risk factors and the other a consequence of the distribution of oral cancer in human populations. In most populations, oral cancer is strongly related to either tobacco use or alcohol consumption or both[11]. Typically, these two risk factors are related to diet, with tobacco users consuming diets that are otherwise less healthy than diets of non-tobacco users[43,44]. As such, these risk behaviours have the potential to confound the apparent effect of dietary factors. Besides relationships among risk behaviours, there are organic relationships among dietary constituents and those related to the use of tobacco. For example, products of tobacco combustion will create a demand for antioxidants, such as β-carotene, whose only source (at least in a population such as this) is dietary. Thus, smoking is an important determinant of serum β-carotene levels, even in subjects who are apparently healthy[45,46]. This demand might be increased in subjects with cancers or precancerous conditions, especially in those who continue to smoke. So, while the use of biomarkers of dietary exposure may have conceptual appeal, tissue levels may not be an adequate reflection of dietary intake (although it may have relevance to tissue-level exposure to the nutrient or its metabolite). In studies using serum levels of β-carotene as a biomarker[47], unless smoking is carefully measured and controlled in analyses, some of the variability in β-carotene levels will be explained by tobacco smoking, and inferences regarding dietary β-carotene almost certainly will be confounded, even in cohort studies of subjects who are apparently healthy when recruited[45,46].

The second obstacle in the design and execution of epidemiological studies is the fact that oral cancer is a rare disease in most populations. Therefore, it has been amenable to study mainly using case–control designs. Such designs are subject to biases in self-report, arising either directly or indirectly from changes in exposure to risk factors, especially diet, concomitant with the onset of disease symptoms[11,19] or to beliefs held by research subjects regarding the causes of disease or disease progression[48]. Because oral cancer is likely to affect the diets of oral cancer patients and diet–cancer hypotheses have been popularised in many populations, such studies are limited by the potential for biased dietary recall among the cases as compared with the controls[11]. Apparently, there is no specific scientific literature on beliefs or attitudes about diet in relation to cancer in India, although there are widely held beliefs about diet and health more generally[49].

In this study, we were careful to enrol only users of

tobacco and then to measure their exposure to tobacco products very carefully using methods that had been developed and refined through years of study in this population[12,50]. In designing this study, a decision was made to focus on precancerous lesions. This was done to increase outcome yield and to reduce the probability of biased dietary exposure estimates due to the presence of a condition that could affect the physical sensation and palatability of food among the cases. Our prior research had indicated a high relative risk of the precancerous lesions seen in this population progressing to frank cancer[14]. By studying these conditions earlier on in the natural history of the disease, there would be a better chance of measuring diet during the more aetiologically relevant period. Finally, in order to reduce further the probability of bias, we chose to withhold the diagnosis of the condition from both the subject and the interviewer until the diet interview was completed (<5 days from the exam).

Oral precancerous lesions included in this study, with the exception of oral submucous fibrosis, produced no symptom that would materially affect the usual diet of the affected individual. Oral submucous fibrosis almost invariably causes a burning sensation on intake of spicy food and since the food in this part of India is especially spicy, that could cause some changes in usual diet. Following the study protocol, oral submucous fibrosis cases were included in the case group even though there were only two and they would not have materially affected findings. It was not feasible to conduct a separate analysis for oral submucous fibrosis, as was done for the Gujarat study[10].

Study findings in context

As expected, the strongest relationship observed was that between reverse *chutta* and palatal lesions, which represented the most common tobacco habit and most common lesion type, respectively. As with other studies in India, there was no affect of reported alcohol exposure[42]. This may be due to the dominance of tobacco use in causing these lesions or to relatively low rates of exposure to alcohol.

Judging by the size of the effect across the interquartile range of exposure (Table 4), the strongest dietary relationships observed in this study were the protective effects of zinc, calcium and fibre. The observed effect of zinc is consistent with that reported in another study in reverse *chutta* smokers[22,25]. Zinc is a necessary component of over 200 enzyme systems necessary for the proper differentiation and growth of cells and as a structural constituent of many proteins, hormones, neuropeptides, hormone receptors and probably polynucleotides[51]. Like zinc, iron showed a linear (though weaker) effect in these data. Also like zinc, iron may be important for proper differentiation of epithelial tissue and other potential mechanisms of carcinogenesis[52–55].

In a hospital-based case–control study in China, it was found that dietary fibre derived from fruits and vegetables showed a strong negative association with oral cancer risk[47]. These results were similar to those from a population-based case–control study in which risks decreased with increasing intake of fruits and some vegetables[27]. In another case–control study in the USA, it was observed that dietary fibre was associated with decreased risk[29]. Calcium, however, had not been observed to have a strong relationship with oral cancer previously. There is some suggestion that Ca^{2+} release affects cell rounding and retraction in human oral cavity epidermoid carcinoma cells[56]. There is one case–control study that reports higher nail concentrations of iron and calcium in oesophageal cancer cases than in controls[57]. Still, these findings pertain to a different site and histological type and, in frank cases of cancer, there may be metabolic alterations that further obfuscate the relationship between diet and disease.

Results of a survey of a population with a high risk of oral and oesophageal cancer (in Uzbekistan) indicated that blood levels of retinal, carotene and riboflavin were lower among individuals with these conditions[28,58]. The use of blood measures in people with frank disease may lead to biased estimates of exposure relative to typical diet in the aetiological period of interest, irrespective of the effect of smoking on tissue levels of antioxidants. Analysing data collected before disease onset, a nested case–control study in Washington County, MD showed that serum levels of carotenoids and α-tocopherol were lower among subjects who developed oral and pharyngeal cancer than in matched controls who were free of disease[59]. Because of its design, that study was able to circumvent problems with disease-related biases[59].

Sodium, ascorbic acid and β-carotene showed some of the lowest correlation and regression coefficients in comparing the FFQ- and 24HR-derived dietary data. Also, these three nutrients were only weakly associated with the lesions, if at all. It may be that these two observations are related; i.e. to some extent imprecision in estimating intake may explain the lack of strong relationship with disease status. In our data, there was a suggestion that β-carotene intake in the highest quartile (here estimated to be $>2.4\,\text{mg day}^{-1}$) may be protective. That this is still far below pharmacological range is consistent with findings from other studies on the effect of β-carotene in the physiological range[23,60–63].

In this study, riboflavin was found to be protective. In one case–control study conducted in Western New York State, riboflavin was associated with increased risk[29]. However, in another case–control study from Italy, an increased maize intake among cases with cancers of the oral cavity, pharynx and oesophagus was reported[30]. Because maize can cause deficiencies of riboflavin, this result is consistent with a broad range of evidence indicating a protective effect of this B vitamin from

studies conducted in Africa, China, the United States and Italy[30].

In an intervention trial of reverse *chutta* smokers from Srikakulam District, using the frequency of micronucleated cells and DNA adducts as indicators of DNA damage, it was reported that supplementation with four nutrients (vitamin A, riboflavin, zinc and selenium) reduced micronuclei and DNA adducts in subjects both with and without precancerous lesions at the beginning of the study[25]. It also was found that these same nutrients were related to a reduced incidence of oral precancerous lesions[22]. In a randomised, double-blind intervention trial conducted in a population with a high incidence of disease in Huixian, People's Republic of China, there was only a weak suggestion of protective effects of riboflavin and zinc[64].

The incident oral precancerous lesions diagnosed during follow-up after one year (39 cases) and an equal number of matched controls examined and interviewed exactly in the same manner as in the case–control study provided a built-in check for the results obtained in the main case–control study. Although the one-year dataset afforded little statistical power, it did provide a unique opportunity to compare point estimates of the OR with those from the main case–control study. When we adjusted the 95% CI for the sample size in the main case–control study we found that they were remarkably similar, indicating that the wide confidence limits were due to small sample size and not heterogeneity of effect. In the main case–control study, no estimate of the duration of the presence of the lesion was possible and there could have been some undetermined heterogeneity with regard to that in the case group. Analysis of these 39 incident cases addressed that problem and it was reassuring that the results were very similar.

Weaknesses and recommendations for future study

Because of the uniformly low level of education in this population, it was not possible to control for it in analyses or to examine covariance in other factors (e.g. dietary calcium) with which it may be related. Future work in this population should aim to enrol subjects with a wider range of educational attainment.

Except for two studies on which we reported from Gujarat[10] and Kerala[9], studies of diet and cancer previously reported from India have used simple diet checklists and FFQs inadequate for the purposes of nutrient estimation. In Andhra Pradesh, a large portion of the adult population is illiterate. This fact, as well as our need to standardise collection methods to the extent possible, compelled us to use the interviewer-administered FFQ. Testing of this instrument was conducted in an external validation study in a population similar to that used as the basis of the case–control study. Results indicated a relatively high level of agreement between nutrient consumption data derived from this FFQ and data derived from eight days of 24HR administered over a one-year period. This was true even for total caloric intake to which rice was a major contributor and occurred despite an obvious miscalibration in reporting intake of rice preparations. The overestimate in rice intake was similar in direction to the social approval bias that we have observed among men in the USA[48,65], but of somewhat larger magnitude. Unlike results in both Gujarat[34] and Kerala[33], the overestimate affected both the 24HR-derived and the FFQ-derived estimates. Given the high level of importance attached to food in India, future work should focus on understanding the source of the bias and methods developed to minimise its effect.

Rather than make *post hoc* adjustments to account for miscalibration, we used the actual values in all analyses. As with most epidemiological studies of diet and cancer in humans, this study produced ORs as estimates of relative risk of exposure to these nutrients and this miscalibration would not affect these estimates. By not adjusting, we have avoided adding possible error to the estimated relative risk. Still, estimating exact nutrient dose–response relationships would be problematic because of the overreporting of rice intake (i.e. real exposure levels would be lower than percentile scores shown in Table 4).

Summary

The results of this study, unencumbered by the kind of biases that normally would beset a study of nutrition and oral cancer, indicate a protective effect of several micronutrients in oral precancerous lesions in a population exposed to tobacco. In its design, we recognised the potential for intractable confounding and took advance remedial steps such as the use of blinded interviews to minimise the possibility of bias associated with diagnosis, referral and assessment procedures. A focus on oral precancerous lesions offered a particularly good opportunity for research since, unlike oral cancer, the individual was generally not aware of the lesion and had few, if any, associated symptoms that might affect dietary intake. Results from this study support consumption of a nutrient-dense, vegetable-based diet in reducing risk of oral precancerous lesions, a conclusion consistent with that reached by a variety of governmental and non-governmental agencies[66–68]. Even though a disease-related bias was unlikely, future work should focus on identifying and controlling for more generalised (i.e. non disease-related) biases in the self-reporting of dietary intake.

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Syllabus: Introduction to Genetic and Molecular Epidemiology

Introduction to Genetic and Molecular Epidemiology
Spring 2002

Instructors:	Xifeng Wu, MD, PhD, Debbie del Junco, PhD, and Corinne Aragaki PhD
Time:	Tuesdays and Thursdays, 5:00 – 7:00
Place:	Interactive Television Room {Dallas: V7-114 (Code: 2951)}
Credit Hours:	4
Prerequisite:	None
Recommended:	Introduction to Epidemiology Introduction to Biometry (or Biostatistics)
Office:	RAS W1022/HMB 2.208 (Wu), RAS W626 (del Junco), V8.112B Dallas (Aragaki)
Office Hours:	By appointment
Phone:	713-745-2485 (Wu), 713-500-9239 (del Junco), 214-648-1054 (Aragaki)
E-mail:	xwu@notes.mdacc.tmc.edu, ddeljunco@sph.uth.tmc.edu, Corinne.Aragaki@UTSouthwestern.edu
Text:	The required texts are Molecular Epidemiology: Principles and Practices by Paul A. Schulte and Frederica P. Perera (Academic Press, Inc., 1993) and Statistics in Human Genetics by Pak Sham (Oxford University Press 1997).
Class Notes:	To offset some xeroxing costs, please pay your local class representative $10 (Debbie in Houston, Corinne in Dallas, and Maria Elena Rodriguez in Brownsville) by the end of the month.
Website:	http://www2.utsouthwestern.edu/publichealth/Aragaki/Classes/index.htm (there's a link to the Genetic and Molecular website, just too cumbersome to type).

1. BACKGROUND AND OBJECTIVES

Companion course to Molecular Epidemiology. Molecular Epidemiology is designed as a survey course for students with a background in genetic epidemiology. If you lack that background or wish to know more about genetic epidemiology, this course will provide context for the molecular epidemiology portion of the class. In addition to an overview of molecular biology, genetics, statistics, and epidemiology, this course will presents methods and techniques for genetic and molecular epidemiology studies. Emphasis will be placed on the application of biomarkers analyses using linkage and linkage disequilibrium. Advantages and limitations of using biomarkers in epidemiologic studies will be discussed.

The objectives of this course are:

1. To enable students to critically review the scientific literature that deals with research and advances in genetic and molecular epidemiology.

2. To enable students to communicate and facilitate interdisciplinary research with geneticists, biochemists, toxicologists, microbiologists, cellular and molecular biologists and other scientists who have research expertise in the measurement of human exposures and disease susceptibility.

3. To enable students to design a valid genetic and molecular epidemiologic study that incorporates relevant biomarkers.

4. To enable students to be able to conduct simple linkage and linkage disequilibrium analyses.

2. EVALUATION:

1. **Lab Assignments** (30%)

Short lab assignments which provide an opportunity to apply the concepts and skills discussed in the lecture will be given. Lab assignments will be discussed in class, and all students will have the opportunity to lead the class discussion. Students will submit individual write-ups for grading.

2. **Class Project** (50%)

All students are expected to complete a final class project. The write-up of the project should be no longer than 15 pages (typed, double-spaced) and will be comprised of the following:

a. *Hypotheses/research question and background.* State not only the research question you intend to answer but also the reasons you are interested in exploring this particular question. Use references to back up the rationale behind your hypothesis.

b. *Study design and justification.* Given your hypothesis/specific aims, design a study and justify design choice.

c. *Sample description.* Describe the study population you are proposing to use to explore your research question. You may want to include a description of the demographic characteristics of your study sample as well as a short discussion about the limitations (if any) of your study sample, especially with respect to generalizability.

d. *Statistical methods.* Identify the statistical method of analysis you will use to answer your research question and provide justification for that choice.

e. *Discussion/comments.* Discuss your proposal with respect to (1) the limitations of your ability to answer your research question as originally proposed; (2) what you found most significant/interesting/innovative about your method. Relate this to your rationale.

You will submit small portions of your project throughout the semester to help us

monitor your progress and make sure you have chosen a manageable project. Although the small assignments will not be graded formally, failure to turn these in will hinder your progress in completing the project and will negatively affect your course participation grade. The due dates associated with the project are as follows

Project proposal - Identify your topic area, data source, and rationale. (1 page). **Due Feb. 14.**

Project outline - Identify the research question(s) you are considering for exploration, the data sources and variables, and the statistical tests and rationale you plan to use for investigating your question(s). (1 page). **Due Mar 28.**

Final project - **Due May 2.**

3. **Class participation or just demonstrated interest in the class** (20%).

4. **Bonus points** (maximum 10%). (½ per term) For each molecular/genetic epidemiology term that you define in writing such that we can include it in the class website.

Policies regarding class assignments:

1. All assignments are due at the beginning of class on the day they are due. Assignments which are received after that time will be subject to an automatic 10% point deduction unless prior arrangements have been made with the course instructor. Requests to turn in assignments at times other than the due date must be submitted to the course instructor in writing prior to the due date. The course instructor will notify the student in writing whether or not the request is approved.

2. Although students may work together on the details of some assignments (i.e., in class work on the lab assignments), students must work independently in preparing the written assignments.

- Final Exam. Short independent project that will consist of writing a design of a molecular epidemiology study. Specific format and requirements for this project will be discussed in class.

Jan. 15, 17	(Wu) Introduction to Molecular Epidemiology Molecular Biomarkers; Classification of Biomarkers (Exposure, Biomarkers, Genetic Biomarkers, Disease Biomarkers, and Intervention Biomarkers)	Course introduction - Basic genetic and molecular concepts review Available databases – gDB, Entrez, OMIM, HuGENet, linkage.rockefeller.edu, etc.
22, 24	(Fraizer) Intro to Molecular Biology (Zhu) Core techniques and applications in molecular epidemiology	**Discuss Lab Assignment #1: Internet information sources** (del Junco) Intro to genetic study design: familial studies/aggregation, twin studies
29, 31	(del Junco) Intro to epidemiology/ Design Considerations in Molecular Epidemiology	Likelihood and statistical conceptual review
Feb. 5, 7	(Amos) Statistical Methods in Molecular Epidemiology (Aragaki) Family Study, and Genetic Epidemiology	Segregation and multiple stage sampling
12, 14	(Aragaki) Gene- Environment Interaction	Study design and simple analysis for Transmission Disequilibrium Test **PROJECT PROPOSAL DUE** **Discuss Lab Assignment #2: Familial studies**
19, 21	(Bondy, Chamberlain) Biosample Banking Ethical Use of Banked Samples, Informed Consent Process for Genetic Information, Application of Risk Information to Cancer Prevention and Control, Moral, Ethical and Legal Issues	TDT and relative designs continued
26, 28	(Wu, Schabath, Zhao) Molecular Epidemiology Laboratory Tutorial **DISCUSS TAKE-HOME MIDTERM**	Introduction to Genehunter preliminaries and Genehunter with TDT
Mar. 5, 7	**SPRING BREAK**	

Mar. 12, 14	(DiGiovanni) Models of Carcinogenesis (Ananthaswamy) UV-Induced Carcinogenesis	Single point linkage analysis
19, 21	(del Junco) Metabolic Genetic Polymorphisms and Cancer Susceptibility (Wu) DNA repair Genetic Polymorphisms and Cancer Susceptibility **MIDTERM DUE**	**Discuss Lab Assignment # 3: TDT** Multipoint linkage analysis
26, 28	(El-Zein) Introduction and basis of cytogenetics (Wu) Genetic Instability and DNA Repair DISCUSS FINAL PROJECT	Nonparametric linkage analysis **PROJECT OUTLINE DUE**
Apr. 2, 4	(Bondy) Identification of Susceptible Populations: Models of Cancer Risk Prediction (Strom) Molecular Epidemiology of Hormonal-related Cancer	(Hanis) High throughput methods for genetic and molecular epidemiology
9, 11	Molecular Epidemiology of Infectious Disease (Hwang) HCV, HBV (Follen-Mitchell) HPV	Other study designs and methods: Case-Only designs, gene-environment studies Genomic techniques – microarrays and others
16, 18	(Lotan) Natural Agents in Cancer Prevention (Cinciripini) Genetic Susceptibility to nicotine addiction	(del Junco) Tying all the pieces together Developing collaborations
23, 25		**Discuss Lab Assignment #4: linkage analysis** Data presentation skills and time to work on projects
Apr. 30, May 2	Student presentations for molecular epi	**FINAL PROJECT DUE**

Syllabus: Nutritional Epidemiology

PH2998: Section: 100
Drs. R. Sue Day and Maureen Sanderson

COURSE DESCRIPTION

PREREQUISITES: (Introduction to Epidemiology and Biometry, or equivalent) Students need to have knowledge of epidemiologic study designs, be able to understand correlations, regression analyses and other statistical measures of agreement, basic nutrition and ability or willingness to learn a statistical software program.

LOCATION AND TIME: Wednesday, Room W-608, 1-4 p.m.

INSTRUCTORS:

R. Sue Day, Ph.D.
Office: W-916
Telephone: 500-9317
FAX: 500-9329
E-Mail: rena.s.day@uth.tmc.edu
Message center: W-914
Office hours by appointment

Maureen Sanderson, Ph.D.
Office: 2.202 A Brownsville
Telephone: 956-554-5162
FAX: 956-554-5152
E-Mail: msanderson@utb.edu
Office hours by appointment

OBJECTIVES:

The objective of the course is to describe and evaluate the issues associated with nutritional assessment of populations using food and nutrient, biochemical and anthropometric data. A combined lecture, seminar and hands-on approach is taken to examine the strengths and weaknesses of the various nutritional assessment methodologies for use with each of the major epidemiological study designs. Epidemiological studies of the relationship of nutrition and chronic diseases are critically evaluated. Students will be given a data set and guided opportunities to explore methodologies of statistical analysis and interpretation of nutritional data as part of the learning experience. Reading material include textbooks and selections from the current literature.

The objectives for the course are:

1. To describe the issues associated with nutritional assessment of populations.

2. To determine the strengths and weaknesses of the various nutritional assessment methodologies for use with the major epidemiologic study designs.

3. To describe the issues associated with utilization of nutrient data base systems.

4. To calculate the number of food records and sample size requirements for nutritional assessments using a nutritional data set.

5. To calculate validity and reliability measurers for a nutritional data set.

6. To compute energy adjusted nutrients using a nutritional data set.

7. To identify potential confounding factors associated with the measurement of food and nutrient intake and its association with disease.

8. To design a nutritional assessment of a given population to address a research question in an epidemiologic study.

9. To evaluate the design and methods used in the nutritional epidemiologic literature.

ASSESSING COMPETENCY:

As with all classes at the School of Public Health the only grades registered will be Pass, Fail, Withdrew, and Incomplete. Comments on student performance will be forwarded to evaluation committees.

To receive a "Pass", a student must:

(1) attend and participate in class,
(2) complete reading assignments,
(3) complete all homework/class assignments with a grade of 70 or greater, and
(4) complete both mid-term and final exams with a grade of 70 or greater.

If a student needs to miss class for any reason, contact the instructor prior to the class or leave a message as soon as possible. Assignments turned in after the 'due date' class will be considered late and points will be deducted from the total. If a student has an arranged absence cleared with the instructor, an acceptable turn in date should be negotiated when the absence is discussed. No assignment will be accepted more than I week late.

Students may withdraw from the course at any time before the final grade is released. An "Incomplete" will be registered only when serious illness or similar unavoidable circumstances have prevented completion of the term project or other assignments.

TEXTBOOKS:

Walter Willett. Nutritional Epidemiology, 2nd edition. Oxford University Press 1998.

Barrie M. Margetts and Michael Nelson (eds). Design Concepts in Nutritional Epidemiology, 2nd edition. Oxford University Press 1997.

Other texts which are available in the library and contain relevant material are:

Rosalind S. Gibson. Principles of Nutritional Assessment. Oxford University Press 1990.

Rosalind S. Gibson. Nutritional Assessment. A laboratory manual. Oxford University Press 1993.

Derrick B. Jelliffe and E. F. Patrice Jelliffe. Community Nutritional Assessment. Oxford University Press 1989.

Nutrient Adequacy: Assessment Using Food Consumption Surveys. National Academy Press 1986.

Smith, J.L. (ed) Nutrient databank directory, 9 Edition, University of Delaware, 1993

Mason, J.B. et al. Nutritional surveillance, WHO, Geneva, 1984

Mayrent, S.L. (ed) (Hennekens) Epidemiology in Medicine, Little, Brown and Company, 1987

Abramson, J.H. Survey Methods in Community Medicine, 4 Edition, Churchill Livingston, 1990

Himes, J.H. (ed) Anthropometric Assessment of Nutritional Status, Wiley-Liss, 1991

Whitehead, R.G. (ed) New Techniques in Nutritional Research Vol.9, Academic Press, 1991

FAQ Conducting Small-scale Nutrition Surveys. A Field Manual. Nutrition in Agriculture #5, 1990

Anderson, S.A. (ed) Guidelines for Use of Dietary Intake Data. Prepared for the Center for Food Safety and Applied Nutrition, FDA, Dept. HHS by Life sciences research office, FASEB, December 1986

Various authors, Dietary Assessment Methods, AJCN, Volume 59, number i(s), 1994

Leaverton, P.E. A Review of Biostatistics. A program for self-instruction, 3 edition, Little, Brown, & Company, 1986

Readings will be available in class or the library for specified topics.

READING LIST

Topic	Book Readings	Articles
1. Introduction	None	
2. Overview	Willett ch. 1,2,10 Margetts ch. 1,7	None
3. Holiday		
4. Causality	Hennekens p. 39-50	

5. Diet assessment	Margetts ch. 5	Anderson 1982 Beaton 1986	
6. Portion sizes	Willett p. 79-83	Guthrie 1984 Samet 1984	Faggiano 1992 Clapp 1991
Data Base	Willett p. 28-32, 56-57 Margetts ch. 4	None	
7. Food records/ recalls	Margetts ch. 6 Willett ch. 4	McPherson 1990	
8-10. Variation & sample size	Willett ch. 3 Margetts p. 57-62	Liu 1978 Nelson 1989 Wassertheil-Smoller 1993 Miller 1991	Beaton 1979 Anderson 1986
11-12. Train/lab	None		
13. Biochemical Assessment	Margetts ch. 7	None	
Stunting, Wasting, And Obesity		None	
14. No class	None		
15. Diet history	Willett ch.7 Margetts ch. 6	Reed 1954 Burke 1957	Friedenreich 1992 Mann 1962
16. FFQ	Willett ch. 5,6	Longnecker 1993 Briefel 1992 Rimm 1992	Block 1994 Sempos 1992 Baghurst 1992
17-18. Train/No class	None		
19. Multicollinearity	Margetts ch.3	Anderson 1986	
Adjusted Kcal Intake	Willett ch. 11	Shekelle 1987 Brown 1994	Willett 1986
20. Validity	Willett ch. 6 Margetts ch.8	Pietinen 1988 Feunekes 1993 Block 1989 Sobell 1989 Thompson 1993	Crawford 1994 van Horn 1993 Block 1990 Treiber 1990
21-22. Reliability	Willett ch. 6	See articles from validity	

	Margetts ch. 8	
23. Lab	None	
24. Sources of error	Margetts ch. 3 Willett ch. 12	Anderson 1986 (repeat)
25. Associations	Hennekens ch. 4 Margetts ch. 9	None
26. Epi. Study designs	Margetts ch. 10-13 Willett ch. 16	Anderson 1986
27-30. Presentations	None	

CLASS SCHEDULE

CLASS	DAY	DATE	TOPIC
1	MON	Jan 5	Introduction
2	WED	Jan 7	Overview of nutrition epidemiology Diet, biochemical and anthropometric assessment
3	MON	Jan 12	Holiday
4	WED	Jan 14	Causality Explanation of term project
5	MON	Jan 19	Dietary assessment of populations
6	WED	Jan 21	Issues concerning portion sizes Food composition tables and nutrient data bases
7	MON	Jan 26	Food records and 24 hour recalls
8	WED	Jan 28	Food records and 24 hour recalls
9	MON	Feb 2	Variation in intake Homework 1 Assigned: Calculation of appropriate number of food records Sample size issues associated with dietary intake Homework 2 Assigned: Calculation of sample sizes
10	WED	Feb 4	Discussion of homework Homework 1 due
11	MON	Feb 9	Explanation of keeping food records

			Classroom coding of food records with FIAS Homework 2 Assigned: Complete food records
12	WED	Feb 11	COMPUTER LABORATORY Coding food records with FIAS
13	MON	Feb 16	Biochemical assessment Clinical assessment of population – stunting, Wasting, and obesity
14	WED	Feb 18	No class – coding of food records
15	MON	Feb 23	Diet history Food frequency questionnaires (part 1) Homework 2 due Research Question Due – Term Project
16	WED	Feb 25	Food frequency questionnaires (part 2)
17	MON	March 1	Train FFQ Interviews Homework 3 Assigned: FFQ Interviews
18	WED	March 3	No Class – FFQ Interviews
19	MON	March 8	Multicollinearity, Energy adjusted intake Homework 3 Due Homework 4 Assigned: Energy adjustment Discuss presentation date for Term Project
20	WED	March 10	Issues of validity
21	MON	March 15	Issues of validity and reliability Homework 4 Due
22	WED	March 17	Issues of reliability
23	MON	March 22	COMPUTER LABORATORY Homework 5 Assigned: Descriptive analysis and Analysis of reliability and validity data
24	WED	March 24	Sources of error: sampling error and information bias Homework 6 Assigned: Sample size
25	MON	March 29	Measures of association in epidemiologic studies And epidemiologic study designs Homework 5 Due

26	WED	March 31	Epidemiologic study designs Presentations Homework 6 Due
27	MON	April 5	Presentations
28	WED	April 7	Presentations
29	MON	April 12	Presentations Term Project Due
30	WED	April 14	Presentations Course evaluation

Grant Abstract

Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women

Gerson Peltz (UTB), Maureen Sanderson (UTSPH-B)

Background: The overall goal of this proposed HBCU/MI Partnership Training Award is to further strengthen the collaborative relationship between the minority institution, University of Texas at Brownsville (UTB), and the collaborating institution, University of Texas-Houston School of Public Health (UTSPH). The UTSPH established a regional campus on the UTB campus in 2001, and the Co-Principal Investigator of the partnership from UTSPH is located in Brownsville. The vision of UTB and the UTSPH Brownsville regional campus is to conduct community-based participatory research in areas deemed important by the community.

Objective/Hypothesis: The proposed training program will focus on breast cancer etiology, specifically the interrelationships between hormones, diet, body size and breast cancer among Hispanic women. We hypothesize that the clinic-based case-control study conducted as part of the training program will be useful in identifying factors associated with decreased breast cancer risk among Hispanic women.

Specific Aims: Specific aims of the proposed training program are: 1) to provide UTB faculty training through classes, presentations and seminars to gain knowledge of epidemiology, proposal development, cancer epidemiology, intervention mapping, field epidemiology, biostatistics, and nutrition epidemiology offered by UTSPH faculty in-person from Brownsville and via ITV from Houston, 2) to design and conduct a clinic-based case-control study to include completion of a questionnaire, anthropometry and a blood draw, 3) to disseminate findings to the Texas Department of Health, the Department of Defense, and local health providers and health clinics, and 4) to submit proposals to conduct larger population-based case-control studies of breast cancer in the Lower Rio Grande Valley.

Study Design: The collaborative arrangement for the HBCU/MI Partnership Training Award will consist of three UTB faculty with no history of breast cancer funding, and six UTSPH faculty with funding histories in breast and others cancers. This proposal is envisioned as occurring in two phases the Training Phase and the Investigation Phase. UTB faculty will undergo intensive training provided by UTSPH faculty during year 1. Additional training will take place in subsequent years. To reinforce training, faculty from UTB and UTSPH will conduct a clinic-based case-control study of breast cancer to investigate its' association with hormones, diet and body size in years 2 and 3. Under the guidance of UTSPH faculty, UTB faculty will submit grants for additional funding using the breast cancer study as preliminary data in year 4.

Relevance: While faculty from UTSPH have expertise in breast cancer research, faculty from UTB have strong ties with the medical and lay community in Brownsville and Cameron County. To date, no breast cancer research has been conducted in Cameron County. By partnering together, these institutions hope to achieve the following goals: 1) develop a regional cancer registry, 2) build infrastructure to conduct population-based case-control studies of breast cancer, 3) initiate studies to investigate factors which may protect Hispanic women from breast cancer, and 4) establish an outstanding breast cancer research program.

Manuscript: Sanderson M, Shu XO, Zheng W. Reply 1: An assessment of the preconceptional mitochondrial hypothesis. Br J Cancer 2003;88:1819-1820.

British Journal of Cancer (2003) 88, 1819–1821

www.bjcancer.com

Reply 1: An assessment of the preconceptional mitochondrial hypothesis

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Sir,

We found Dr van Noord's preconceptional mitochondrial hypothesis interesting particularly in line with a recent report linking polymorphisms of two DNA base excision repair genes (XRCC1 and hOGG1) to breast cancer risk in daughters born to older mothers (Hodgson *et al*, 2003). Manganese superoxide dismutase (MnSOD) may impair the mitochondria's ability to reduce oxidative stress (Oberley and Oberley, 1997). MnSOD has been linked to breast cancer (Ambrosone *et al*, 1999), and may be another pathway through which older maternal age may function. Further support for this hypothesis comes from a recent study that found mitochondrial DNA damage in breast cancer tissue (Richard *et al*, 2000).

To test this hypothesis, we analysed the association of parental age with breast cancer risk using data from the Shanghai Breast Cancer Study (SBCS), and the results are in shown Table 1. After adjustment for established breast cancer risk factors and pregnancy order, we did not find an association between older maternal or paternal age and premenopausal breast cancer in our low-risk population. Additional adjustment for paternal age resulted in a nonsignificantly elevated risk of breast cancer associated with older maternal age. All perinatal information was based on maternal report.

Although we collected information on whether the mother had a threatened miscarriage with the index pregnancy, too few women reported this adverse event (six case mothers, 13 control mothers) to provide a stable risk estimate. Other studies may have sufficient numbers of mothers to investigate this aspect of Dr van Noord's hypothesis.

Dr van Noord argued that insulin-like growth factor- I (IGF-1) might be unlikely to explain the inconsistent findings on birth weight and breast cancer risk in the literature, since the link between IGF-I and breast cancer risk has been found primarily in premenopausal women, while the high birth weight-breast cancer association has been seen among pre- and postmenopausal women. A previous report from the SBCS showed that elevated levels of IGF-I were associated with an increased risk of breast cancer among all women, but the association was more pronounced among women diagnosed premenopausally and among women with a high body mass index or waist-to-hip ratio (Yu *et al*, 2001). We found in a large US study that high birth

Table 1 Odds ratios of breast cancer associated with maternal age and paternal age

	Cases ($n=288$)	Controls ($n=350$)	OR[a]	(95% CI)	OR[b]	(95% CI)
Maternal age (years)						
<25	73	98	1.0	(referent)	1.0	(referent)
25–29	123	127	1.4	(0.8–2.3)	1.6	(0.9–2.7)
30–34	63	77	1.1	(0.6–2.0)	1.5	(0.8–2.9)
⩾35	29	47	1.1	(0.5–2.2)	1.6	(0.7–3.9)
P trend			$P=0.84$		$P=0.34$	
Paternal age (years)						
<25	34	41	1.0	(referent)	1.0	(referent)
25–29	96	94	1.4	(0.7–2.8)	1.3	(0.6–2.7)
30–34	88	103	1.3	(0.7–2.7)	1.2	(0.6–2.6)
⩾35	70	111	0.9	(0.4–1.9)	0.7	(0.3–1.8)
P trend			$P=0.13$		$P=0.08$	

[a]Adjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, age at first live birth, and pregnancy order. [b]Adjusted for age, income, family history of breast cancer in first-degree relative, history of fibroadenoma, age at menarche, parity, age at first live birth, pregnancy order, and maternal age or paternal age.

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weight was associated with an elevated risk among premenopausal women (OR = 1.7, 95% CI 1.1–2.5), but a nonsignificantly reduced risk among postmenopausal women (OR = 0.6, 95% CI 0.3–1.1) (Sanderson *et al*, 1996). Therefore, IGF-I as a potential explanation for the birth weight-breast cancer relationship cannot be ruled out.

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Reply 2: Birth weight as a predictor of breast cancer: a case–control study in Norway

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Sir,

We welcome the comments of van Noord concerning the different results for birth weight and breast cancer risk reported by ourselves (Vatten *et al*, 2002) and Sanderson *et al* (2002). He suggests that women's breast cancer risk is influenced by the preconception viability of their mothers' oocytes, particularly the quality of their mitochondria, since mitochondrial quality declines with age. Therefore, van Noord proposes that maternal age at birth is positively associated with breast cancer risk, suggesting that we reanalyse our data to test this hypothesis.

Reliable information on maternal age at birth was available in the Trondheim data, and hence this analysis is based on 186 breast cancer cases and 662 age-matched controls. We used conditional logistic regression to explore the association between the risk of breast cancer and maternal age at birth, and the estimated odds ratios are adjusted for age at first birth and parity. As shown in Table 1, we found no association with breast cancer risk over the four categories of maternal age at birth.

Table 1 Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer associated with maternal age at birth

Variable	Case patients	Control subjects	OR[ab]	95% CI
Maternal age at birth				
<25	56	196	1.0	Reference
25–29	60	212	1.0	0.7–1.5
30–34	41	155	1.0	0.6–1.5
⩾35	29	99	1.0	1.6–1.6
			P trend = 0.97	

[a]ORs are computed using conditional logistic regression with cases and controls matched on year of birth. [b]ORs are adjusted for age at first birth and parity in the regression model.

Although van Noord has proposed an interesting hypothesis, we found no evidence to support that maternal age at birth is positively associated with breast cancer risk. In light of our original findings, that both birth weight and birth length are positively associated with breast cancer risk, important mechanisms linking birth characteristics to breast cancer may be related to foetal growth. Recent research has shown that both birth weight and maternal pre-eclampsia are associated with adolescent growth and maturation (Vatten *et al*, 2003), and therefore, the intrauterine environment may initiate a tracking pattern of growth that ranges throughout childhood and adolescence. Ultimately, this may play a critical role in the development of breast cancer.

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Grant Abstract

Urinary Excretion of Phytoestrogen and Breast Cancer among Hispanic Women

Gerson Peltz

Phytoestrogen intake, measured as dietary consumption of phytoestrogens or as urinary excretion of phytoestrogens, has been found to be protective against breast cancer, especially in populations that consume large amounts of soy. Despite possessing many risk factors for breast cancer, Hispanic women have a relatively low incidence of the disease. A possible explanation for the lower risk of breast cancer among Hispanic women is their high consumption of grains rich in phytoestrogens. We hypothesize that high phytoestrogen intake, as measured by urinary excretion of phytoestrogen, will be protective against breast cancer in a population of Hispanic women. We propose to add urine collection and assessment of urinary excretion of phytoestrogen, another measure of phytoestrogen intake to the ongoing South Texas Women's Health Project, to more accurately reflect consumption of phytoestrogen-rich foods by women in our population. Specific aims of the proposed pilot project are: 1) to determine phytoestrogen intake by measuring urinary excretion of phytoestrogens on a sub-sample of 400 cases and 400 controls participating in our ongoing case-control study of breast cancer, 2) to investigate association between dietary consumption of phytoestrogen, urinary excretion of phytoestrogen, and blood levels of hormones and growth factors among controls, and 3) to evaluate whether phytoestrogen intake reduces breast cancer risk. We will add urine collection from subjects to the ongoing South Texas Women's Health Project. We will perform assays on urinary excretion of phytoestrogen on a sub-sample of 400 cases and 400 controls. We will conduct statistical analyses to evaluate phytoestrogen intake and its relation with hormones, growth factors and breast cancer. The proposed pilot project to be conducted within an ongoing case-control study will be one of very few breast cancer studies that have focused on Hispanic women. The identification of protective factors against breast cancer among Hispanic women may contribute to our understanding of the biological mechanisms of the disease.

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Lifestyle and prostate cancer among older African-American and Caucasian men in South Carolina

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Key words: case–control studies, lifestyle, prostate cancer.

Abstract

Objective: We investigated the association between lifestyle and prostate cancer risk among Caucasian and African–American men, separately.
Methods: This population-based case–control study of prostate cancer among men aged 65–79 years was conducted between 2000 and 2002 in South Carolina. Telephone interviews were completed with 416 incident prostate cancer cases ascertained through the South Carolina Central Cancer Registry, and 429 controls identified through the Health Care Financing Administration Medicare beneficiary file (with respective response rates of 71% and 64%).
Results: Caucasian men working in production, transportation, and material moving had increased prostate cancer risk (odds ratio [OR] = 2.04, 95% confidence interval [CI] 1.17–3.54), while African-American men in the military had reduced prostate cancer risk (OR = 0.19, 95% CI 0.05–0.76). Having five or more prostate specific antigen (PSA) tests within the past five years was associated with prostate cancer among Caucasian men; however, African-American men with prostate cancer tended to have fewer PSA tests. Increasing lycopene consumption was associated with a reduced risk of prostate cancer among Caucasian men ($p = 0.03$), but not among African–American men.
Conclusions: In this population-based case–control study conducted in South Carolina we did not find marked differences in lifestyle factors associated with prostate cancer by race.

Introduction

Prostate cancer is the most frequently diagnosed cancer in the US, and the second leading cause of cancer deaths among men. From 1996 to 2000, the age-adjusted incidence was 65% higher in African-American men than in white men (276.8 *vs.* 167.5 per 100,000) and mortality was 140% higher (73.0 *vs.* 30.2 per 100,000) [1]. From 1992 to 1999, African-American men were 5% less likely to survive beyond five years after diagnosis than white men [1]. This disparity in survival continues to exist at each stage of disease, even when financial barriers have been removed [2, 3].

Little is understood about the etiology of prostate cancer nor do we know what factors might explain why African-American men are at greater risk relative to white men. Age is the strongest risk factor for prostate cancer, and the occurrence of prostate cancer before age 45 is rare [1, 4]. Family history of prostate cancer has been identified as a risk factor for prostate cancer in both case–control studies [5, 6] and cohort studies [7, 8]. There is conflicting evidence on the relation between prostate cancer and risk factors such as obesity, diet, and physical inactivity [4]. Few studies have had sufficient numbers of African-American men to examine risk factors for prostate cancer by race [3, 5, 6, 9–13]. The purpose of this analysis was to investigate the

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association between lifestyle and prostate cancer risk among African-American and Caucasian men, separately.

Materials and methods

This population-based case–control study was conducted in South Carolina from 2000 to 2002. Cases diagnosed with primary invasive prostate cancer between October 1999 and September 2001 were identified through the South Carolina Central Cancer Registry (SCCCR). To ensure that a majority of cases were identified during the study period, a rapid case ascertainment procedure was developed and implemented between hospitals, pathology laboratories, and the SCCCR. Eligible cases were South Carolina residents, aged 65–79, whose prostate cancer was histologically confirmed, and whose physicians had given permission for research staff to contact their patient. During the study period, a total of 755 Caucasian men and 384 African-American men with localized disease (stages I and II), and 144 Caucasian men and 81 African-American men with advanced disease (stages III and IV) were reported to the SCCCR. Of these, 551 Caucasian men and 245 African-American men with localized disease, and 98 Caucasian men and 70 African-American men with advanced disease met the eligibility criteria. We selected all eligible cases with advanced disease, and a random sample of men with localized disease within five-year age group (42% of Caucasian men and 83% of African-American men). A total of 426 prostate cancer cases (70.6% of eligible cases) completed a standardized telephone interview. Of potentially eligible cases, 71 refused (11.8%), 24 died prior to the interview (4.0%), 59 were not located (9.8%), and 23 were too sick to participate (3.8%). A greater percentage of Caucasian cases (75.8% localized and 71.4% advanced) than African-American cases (68.5% localized and 45.7% advanced) completed the interview.

Control subjects were randomly sampled from the 1999 Health Care Financing Administration (HCFA) Medicare beneficiary file. Controls were frequency matched to cases on age (five-year age groups), race (Caucasian, African-American), and geographical region (western, middle and eastern third of the state). Eligible controls were South Carolina residents, aged 65–79, with no history of prostate cancer. A total of 482 control subjects (63.8%) completed the interview. Of potentially eligible controls, 108 refused (14.3%), 22 died prior to the interview (2.9%), 112 were not located (14.8%), and 32 were too sick to participate (4.2%). Caucasian controls (69.6%) were more likely than African-American controls (52.2%) to complete the interview.

After eliminating 59 subjects (7 cases and 52 controls) who had prevalent prostate cancer and three subjects (2 cases and 1 control) who completed fewer than five questions, the final sample size was 845 subjects (416 cases, 429 controls). Of those, 11 cases and 36 controls completed questions on age, race, education, cancer history, history of benign prostatic hyperplasia, and prostate-specific antigen and digital rectal exam screening only, resulting in 407 cases and 393 controls for most analyses.

Institutional Review Boards of the University of South Carolina, the Centers for Disease Control and Prevention, and the National Cancer Institute approved this project's data collection procedures. Cases and controls were recruited through mailings that described the study and informed the potential participant that an interviewer would call them soon. Since the HCFA file does not contain telephone numbers, controls whose telephone numbers could not be located through directory assistance, telephone or reverse directories were sent an additional letter asking for a preferred contact number.

Interviewing began in June 2000 and was completed in August 2002. Trained interviewers from the University of South Carolina Survey Research Laboratory conducted computer-assisted telephone interviews with subjects who provided consent with the understanding that written consent would be obtained. The questionnaire collected information on demographic characteristics, socioeconomic status, stress, coping, alcohol and tobacco use, physical activity, diet, medical history, family history of cancer, history of sexually transmitted infections, and farm-related work activities and exposures. Most exposures pertained to the period prior to a reference date, the date of diagnosis for cases and an assigned date for controls comparable to the date of diagnosis for the cases. The telephone interview took approximately 30–40 min to complete. We pilot tested the study protocol and questionnaire on 20 cases and 20 controls.

We used unconditional logistic regression to estimate the relative risk of prostate cancer associated with lifestyle factors while controlling for potential confounding factors [14]. Race, age, geographical region, educational level, annual income, marital status, occupation, family history of prostate cancer, body mass index (BMI), prostate cancer screening history, diet, physical activity, and alcohol and tobacco use as categorized in Tables 1–4 were evaluated as confounders of lifestyle factor-prostate cancer relations. Usual

Table 1. Comparison of cases and controls for demographic factors by race

	Caucasian		African-American	
	Cases (n = 241) *N* (%)	Controls (n = 227) *N* (%)	Cases (n = 166) *N* (%)	Controls (n = 166) *N* (%)
Stage[a]				
I/II	175 (71.4)		139 (81.3)	
III/IV	70 (28.6)		32 (18.7)	
Age (years)[a]				
65–69	110 (44.9)	111 (43.0)	82 (48.0)	75 (43.9)
70–74	79 (32.2)	73 (28.3)	55 (32.2)	52 (30.4)
75–79	56 (22.9)	74 (28.7)	34 (19.9)	44 (25.7)
Geographical region[a]				
Eastern	146 (59.6)	155 (60.1)	89 (52.1)	88 (51.5)
Middle	49 (20.0)	46 (17.8)	58 (33.9)	46 (26.9)
Western	50 (20.4)	57 (22.1)	24 (14.0)	37 (21.6)
Educational level[a]				
Elementary education	27 (11.2)	24 (9.3)	79 (46.5)	65 (38.0)
Some high school	23 (9.5)	30 (11.6)	32 (18.8)	39 (22.8)
High school graduate	71 (29.3)	71 (27.5)	30 (17.7)	31 (18.1)
Some college or technical school	39 (16.1)	59 (22.9)	15 (8.8)	18 (10.5)
College graduate	82 (33.9)	74 (28.7)	14 (8.2)	18 (10.5)
Missing	3	0	1	0
Annual income				
< $20,000	43 (19.6)	38 (19.0)	79 (58.5)	68 (51.9)
$20,000–$29,999	49 (22.3)	34 (17.0)	23 (17.0)	24 (18.3)
$30,000–$39,999	31 (14.1)	35 (17.5)	11 (8.2)	19 (14.5)
$40,000–$49,999	18 (8.2)	27 (13.5)	7 (5.2)	9 (6.9)
≥ $50,000	79 (35.9)	66 (33.0)	15 (11.1)	11 (8.4)
Missing	21	27	31	35
Marital status				
Single/separated/divorced/ widowed	34 (14.2)	36 (15.9)	39 (24.2)	44 (27.3)
Married/living as married	206 (85.8)	191 (84.1)	122 (75.8)	117 (72.7)
Missing	1	0	5	5

[a] Consists of 245 Caucasian cases and 258 Caucasian controls, and 171 African-American cases and 171 African-American controls.

occupation, based on the longest paying job since respondents were age 14 years, was aggregated into major groups using the 1998 Standard Occupational Classification [15]. BMI, defined as self-reported weight (kg) before reference date divided by the square of self-reported height (m^2), was categorized using quartile distributions among controls. Diet was assessed in a 20-item food frequency questionnaire and pertained to foods consumed at least once a year. Although none of the men indicated their diet had changed since the reference date, they were asked to recall their diet for the period immediately prior to the reference date. Foods on the questionnaire that contributed to the animal fat food group were eggs, whole milk, cheese, ice cream, beef, stew, mixed meat dishes, hot dogs, luncheon meats, bacon, other pork, liver, and chicken; to the dairy food group were whole milk, cheese, and ice cream, and to the lycopene food group were raw tomatoes, cooked tomatoes, and watermelon. Servings per week of food groups were categorized into quartiles among controls. Foods chosen for the food frequency questionnaire were based on those utilized in a prostate cancer study conducted in the late 1980's by Hayes *et al.* [16] among Caucasian and African-American men in three metropolitan areas of the US. Their 60-item food frequency questionnaire was developed by analyzing 24-hour recalls of Caucasian and African-American participants in the National Health and Nutrition Examination Survey I. The present study used 13 of the 17 foods used by Hayes *et al.* for animal fat (missing foods were salt pork, gravy, and half and half; chicken was not separated into baked and fried) and three of the five foods used for lycopene (missing foods were tomato sauce or spaghetti sauce, and tomato juice). Engaging in strenuous or moderate leisure-time physical activity for an average of one or more hours a week since age 18 years were categorized

Table 2. Odds ratios for prostate cancer associated with demographic and medical factors

	Cases (n = 407)	Controls (n = 393)	Combined OR[a]	95% CI	OR Caucasian[b]	OR African-American[b]
Occupation						
Management, professional and related	96	95	1.00	Referent	1.00	1.00
Service	21	13	1.65	0.76, 3.58	2.64	1.10
Sales and office	45	70	0.67	0.42, 1.08	0.56	1.07
Natural resources, construction and maintenance	74	74	1.06	0.68, 1.65	0.98	1.04
Production, transportation, and material moving	134	96	1.60	1.06, 2.40	2.04[c]	1.18
Military	24	39	0.60	0.33, 1.08	0.84	0.19[c]
Missing	13	6				
Family history						
None	278	329	1.00	Referent	1.00	1.00
First-degree	86	43	2.34	1.57, 3.48	2.29[c]	2.40[c]
Second-degree	34	17	2.33	1.27, 4.26	4.44[c]	0.90
Missing	9	4				
Body mass index (quartiles)						
<24.4	90	90	1.00	Referent	1.00	1.00
24.4–27.2	114	101	1.11	0.74, 1.66	1.02	1.27
27.3–29.8	96	96	0.95	0.63, 1.44	0.93	0.98
≥ 29.9	96	96	0.92	0.61, 1.41	1.10	0.79
Missing	11	10				
p for trend			0.98		0.67	0.61
Number of prostate specific antigen tests in past 5 years[d]						
0	61	98	1.00	Referent	1.00	1.00
1–2	68	64	1.62	0.99, 2.65	1.22	2.37[c]
3–4	67	66	1.49	0.91, 2.42	1.15	2.10[c]
≥ 5	157	110	2.16	1.46, 3.33	2.14[c]	1.79
Unknown	63	90	1.03	0.63, 1.66	0.71	1.37
Missing	0	1				
p for trend			0.26		0.30	0.55
Number of digital rectal exams in past 5 years[d]						
0	47	58	1.00	Referent	1.00	1.00
1–2	66	93	0.73	0.43, 1.24	0.70	0.75
3–4	80	84	0.96	0.57, 1.62	1.09	0.88
≥ 5	205	169	1.27	0.79, 2.06	1.25	1.44
Unknown	18	23	0.96	0.43, 2.13	0.56	1.33
Missing	0	2				
p for trend			0.06		0.18	0.10
History or gonorrhea						
No	358	356	1.00	Referent	1.00	1.00
Yes	43	33	1.27	0.77, 2.08	1.62	1.20
Missing	6	4				
History of syphilis						
No	397	383	1.00	Referent	1.00	1.00
Yes	3	4	0.60	0.13, 2.82	–	0.70
Missing	7	6				

[a] Adjusted for race, age, geographic region and family history of prostate cancer.
[b] Adjusted for age, geographic region and family history of prostate cancer.
[c] $p < 0.05$.
[d] Consists of 416 cases and 429 controls.

Table 3. Odds ratios for prostate cancer associated with diet and physical activity

	Cases (n = 407)	Controls (n = 393)	Combined OR[a]	95% CI	OR Caucasian[b]	OR African-American[b]
Consumption of animal fat (quartiles of servings per week)						
≤12.7	90	82	1.00	Referent	1.00	1.00
12.8–18.95	100	79	1.15	0.75, 1.76	1.53	0.75
18.96–26.7	95	83	1.00	0.65, 1.53	1.11	0.84
≥26.8	68	78	0.78	0.49, 1.20	0.69	0.82
Missing	54	71				
p for trend			0.24		0.16	0.84
Consumption of dairy (quartiles of servings per week)						
≤2.2	105	91	1.00	Referent	1.00	1.00
2.3–5.0	102	102	0.84	0.56, 1.24	0.82	0.86
5.1–8.5	75	72	0.83	0.53, 1.28	0.60	1.29
≥8.6	94	86	0.93	0.61, 1.40	0.84	1.04
Missing	31	42				
p for trend			0.59		0.21	0.57
Consumption of lycopene (quartiles of servings per week)						
≤2.6	98	86	1.00	Referent	1.00	1.00
2.7–4.5	97	85	0.98	0.64, 1.49	0.88	1.01
4.6–8.0	96	80	1.04	0.68, 1.59	0.98	1.08
≥8.1	76	84	0.71	0.46, 1.08	0.55[c]	0.99
Missing	40	44				
p for trend			0.32		0.03	0.36
Strenuous physical activity (tertiles among active in hours per week)						
None	218	189	1.00	Referent	1.00	1.00
≤2.0	40	56	0.64	0.41, 1.02	0.50[c]	1.02
2.1–4.0	42	54	0.70	0.44, 1.11	0.87	0.40
≥4.1	83	60	1.18	0.80, 1.76	0.94	1.87
Missing	24	34				
p for trend			0.60		0.48	0.86
Moderate physical activity (tertiles among active in hours per week)						
None	85	86	1.00	Referent	1.00	1.00
≤3.0	70	67	0.95	0.59, 1.51	0.68	1.47
3.1–6.0	109	103	0.97	0.64, 1.49	0.88	0.98
≥6.1	102	94	1.01	0.66, 1.56	0.88	1.12
Missing	41	43				
p for trend			0.39		0.71	0.37

[a] Adjusted for race, age, geographic region and family history of prostate cancer.
[b] Adjusted for age, geographic region and family history of prostate cancer.
[c] $p < 0.05$.

as none and as tertiles within the active group. Using a 10% change between unadjusted and adjusted odds ratios as evidence of confounding, analyses were adjusted for age, geographic region and family history of prostate cancer. The combined analysis was also adjusted for race. Interaction terms between race and lifestyle factors were included to examine whether there was evidence of effect measure modification. Linear trend was assessed by treating categorical variables as continuous variables; for BMI, diet and physical activity, scores were assigned to the median value within quartiles.

Results

Table 1 compares demographic factors of cases and controls separately by race. Although there was no statistical evidence of effect measure modification, analyses are presented separately by race since the effect

Table 4. Odds ratios for prostate cancer associated with alcohol and tobacco use

	Cases (n = 407)	Controls (n = 393)	Combined OR[a]	95% CI	OR Caucasian[b]	OR African-American[b]
Alcohol use						
Never	130	110	1.00	Referent	1.00	1.00
Former	154	139	0.96	0.67, 1.36	0.76	1.24
Current	117	138	0.69	0.47, 1.00	0.60	0.86
Missing	6	6				
Drinks per day						
0	130	110	1.00	Referent	1.00	1.00
1–2	77	65	1.01	0.66, 1.55	0.95	1.09
3–4	33	47	0.60	0.35, 1.01	0.64	0.53
≥5	141	135	0.86	0.60, 1.24	0.66	1.43
Missing	26	36				
p for trend			0.29		0.78	0.15
Drinking duration (years)						
0	130	110	1.00	Referent	1.00	1.00
<25	75	74	0.84	0.55, 1.28	0.84	0.86
25–45	94	87	0.96	0.64, 1.43	0.62	1.84
>45	87	93	0.79	0.53, 1.18	0.69	0.95
Missing	21	29				
p for trend			0.96		0.55	0.35
Smoking status						
Never	106	116	1.00	Referent	1.00	1.00
Former	229	208	1.15	0.83, 1.60	1.20	1.10
Current	67	64	1.13	0.73, 1.75	1.20	1.08
Missing	5	5				
Cigarettes per day						
0	106	116	1.00	Referent	1.00	1.00
<20	146	118	1.32	0.91, 1.90	1.48	1.17
20	78	79	1.03	0.68, 1.57	1.10	0.98
>20	69	64	1.08	0.70, 1.69	1.10	1.17
Missing	8	16				
p for trend			0.79		0.63	0.71
Smoking duration (years)						
0	106	116	1.00	Referent	1.00	1.00
<25	116	109	1.12	0.77, 1.64	1.29	0.93
25–45	103	93	1.11	0.75, 1.65	1.07	1.25
>45	75	67	1.24	0.81, 1.90	1.33	1.17
Missing	7	8				
p for trend			0.55		0.93	0.29

[a] Adjusted for race, age, geographic region and family history of prostate cancer.
[b] Adjusted for age, geographic region and family history of prostate cancer.

of some factors on prostate cancer was on either side of the null value. Compared to controls prostate cancer cases were more likely to be younger and have a lower household income. Caucasian cases tended to be better educated, while African-American cases tended to be less educated.

The odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer associated with demographic and medical factors for all cases and controls, and among Caucasian and African-American men separately are shown in Table 2. The distribution of factors by race differed for occupation (African-Americans were more likely to work in production), BMI (African-Americans were more likely to be in the upper quartile), prostate cancer screening (African-Americans were less likely to have had a PSA test or digital rectal exam), and sexually transmitted infections (African-American men were more likely to have a history of gonorrhea or syphilis). Caucasian men employed in a production occupation had an increased prostate cancer risk (OR = 2.04, 95% CI 1.17–3.54), but African-American men who worked in the military were at reduced risk of prostate cancer (OR = 0.19, 95% CI 0.05–0.76). More than two-fold elevations in risk were seen for family history of prostate cancer in a first-degree relative for all men (OR = 2.34; 95% CI 1.57–3.48), and for Caucasian

(OR = 2.29; 95% CI 1.36–3.85) and African–American (OR = 2.40; 95% CI 1.28–4.51) men. An increased prostate cancer risk was seen for Caucasian men who had five or more PSA tests (OR = 2.14, 95% CI 1.20–3.83) and African-American men who had one–two PSA tests (OR = 2.37, 95% CI 1.14–4.90) and three–four PSA tests (OR = 2.10, 95% CI 1.02–4.34) in the past five years.

Risk of prostate cancer associated with diet and physical activity is presented in Table 3. The distribution of factors by race differed for lycopene (African-American were more likely to be in the lowest quartile) and physical activity (African-Americans were less likely to have engaged in strenuous or moderate activity). Consumption of animal fat, dairy or lycopene among all men was not related to prostate cancer risk. Caucasian men in the highest quartile of lycopene consumption had a 45% reduction in prostate cancer risk (95% CI 0.31–0.98), and there was a trend of decreasing prostate cancer risk with increasing lycopene consumption ($p = 0.03$). Neither strenuous nor moderate physical activity was associated with prostate cancer risk for all men. Among Caucasian men, the reduced risk of prostate cancer seen for two or fewer hours per week of strenuous physical activity did not hold for more hours of strenuous physical activity.

Table 4 presents prostate cancer risk associated with alcohol and tobacco use. The distribution of factors by race differed for drinking and smoking (African-Americans were less likely to be current drinkers and less likely to be former smokers). There were no significant findings for drinking or smoking and prostate cancer risk in our study.

Discussion

Using broad groups to categorize usual occupation we saw an increased risk for prostate cancer among Caucasian men employed in production, transportation and material moving, and a decreased risk among African-American men who worked in the military. We also saw a non-significant increase in prostate cancer risk for Caucasian men employed in service (OR = 2.64, 95% CI 0.82–8.48). Krstev *et al.* [17] reported elevated prostate cancer risks among African-American men, but not Caucasian men, for plant and system operators (OR = 4.06) and other laborers (OR = 1.37) (which are within our production occupations category), and African-American and Caucasian men employed in service (OR = 1.41). They attributed these findings to potential exposure to polycyclic aromatic hydrocarbons. The reduced risk we saw associated with military occupation for African-American men has not been seen elsewhere; [18] however, the numbers of men in this category were quite small (3 cases, 14 controls).

In agreement with several studies, we found more than a two-fold elevation in prostate cancer risk associated with a first-degree (father, brothers, sons) family history of prostate cancer among all men, and among Caucasian and African-American men [5–8]. As was the case with two previous case–control studies, the increase in risk did not differ by race [5, 6]. It should be noted that 70% of cases did not have a family history of prostate cancer; thus, this risk factor affected relatively few men.

We failed to find an association between BMI and prostate cancer as has been the case in the majority of case–control and cohort studies that investigated this relation [19]. Only three of these studies included African-American men, [9, 10, 20] and the two that reported associations for African-American men separately found no association [9, 20]. Although weight and height were based on self-report, it is interesting to note that twice the percentage of African-American controls (35.7%) were in the highest quartile of BMI compared with Caucasian controls (17.7%). This is consistent with the higher prevalence of obesity in African-American men [21].

Our finding of increased risk of prostate cancer among Caucasian men who had five or more PSA tests in the past five years was not unexpected since these men may have undergone work-ups for symptoms related to benign prostate hyperplasia (BPH) [22]. We examined Caucasian cases who had five or more PSA tests by history of BPH; the percentage with a history of BPH (58.9%) did not differ substantially from the percentage without a history of BPH (38.4%), which would argue against detection bias. In contrast, we saw elevated prostate cancer risks among African-American men who had one–four PSA tests in the past five years. A possible explanation for this finding is that African-American men may have been less likely to undergo annual screening due to issues of health care access. When we restricted our analysis to men age 70 years and over who would have been eligible for Medicare for the previous five years, the associations were more pronounced. Thus, in agreement with other studies, African-American men in our study were less likely to be screened regardless of the availability of health insurance [11].

We found no association between a history of sexually transmitted infections and prostate cancer risk. This is in contrast to a meta-analysis that reported significantly elevated pooled odds ratios for gonorrhea and syphilis [23]. Hayes *et al.* [24] reported elevated risks of prostate cancer associated with a history of gonorrhea or syphilis that were similar for African-American and Caucasian men. Although the percentage of Caucasian men in our

study reporting a history of STI was comparable to that reported by Hayes *et al.*, the percentage of African-American men was lower indicating there may have been underreporting of this sensitive topic.

Although we saw no relation between consumption of animal fat or dairy and prostate cancer risk, we saw a reduced risk among Caucasian men who consumed the highest quartile of lycopene and a significant trend of decreasing risk with increasing consumption. Findings from case–control and cohort studies on animal fat [25] and lycopene [26] have been inconsistent; however, dairy has been linked to increased prostate cancer risk in the majority of studies on this topic [27]. In the case–control study we used to design our food frequency questionnaire, Hayes *et al.* [16] assessing Caucasian and African-American men separately, reported significant trends and elevations in risk in the highest quartile of animal fat intake among African-Americans, but not Caucasians. After restricting the analysis to advanced cancer, significant trends and elevations were seen for both groups. Hayes *et al.* [16] failed to find an association between consumption of dairy or lycopene and prostate cancer risk. Restriction of our analysis to advanced cancers did not change our results (data not shown).

Among Caucasian men we found a decreased prostate cancer risk associated with two or fewer hours per week of strenuous physical activity that was not seen for men engaging in more hours per week of strenuous physical activity. Evidence for a protective effect of occupational and/or recreational physical activity on prostate cancer risk has been weak [28]. One case–control study reported a borderline significant reduced risk of prostate cancer associated with physical activity among Caucasian men, but not among African-American men [12], while another study found no association [20]. Although we provided examples of different types of strenuous (*e.g.*, moving heavy things, digging, running, playing basketball) and moderate (*e.g.*, brisk walking, fishing, gardening, playing baseball) physical activity, the time period was since age 18 years, which may have introduced misclassification.

We found no association between ever use, amount and duration of alcohol use and prostate cancer risk. This finding agreed with most studies that reported no association [29]. The one study that investigated the relation separately by race reported a positive association between consumption of large quantities of alcohol and prostate cancer risk that was similar for African-American and white men, and was independent of smoking [30].

In agreement with the majority of studies on this topic, [31] we saw no association between current smoking and prostate cancer risk. Two cohort studies have shown an elevated risk of advanced disease associated with smoking [32, 33]. When we investigated the association between smoking and advanced prostate cancer we still saw no effect (data not shown). The two studies investigating race as an effect modifier of the relation between smoking and prostate cancer were split, with the first case–control study showing no association in either race [34], and the second cohort study showing similarly elevated risks for both races [13].

This study was not without limitations. Our response rates were lower than desired, especially among African-Americans, somewhat limiting the generalizability of our results. The refusal rates by race were not different yet the proportion that could not be located was higher among African-American than Caucasian cases and controls. The range of months from time of diagnosis to interview was 1.8–25.2 (median = 7.2 months). This may have led to misclassification, especially for the 20% of men who recalled events that occurred more than one year ago. Another source of misclassification was the memory problems common in men age 65 years and over. Although our food frequency questionnaire was based on the one utilized by Hayes et al. [16] that was designed to capture the Caucasian and African-American diets, we used fewer foods which may have led to misclassification and prevented us from performing energy adjustment. It is likely that this misclassification was nondifferential, thereby reducing our ability to identify weak associations. Our study power was limited for some main effects and due to small numbers, we were unable to assess effect modification by family history or stage of disease within race.

Our study is the first population-based case–control study of prostate cancer conducted in a rural Southeastern state that included both Caucasian and African-American men. South Carolina has had one of the highest incidence rates of prostate cancer in recent years [35]. Given that apart from age, family history would appear to be the only established risk factor for prostate cancer, [5–8], studies of genetic factors are the logical next step. It is likely that gene–environment interactions will be important in explaining prostate cancer risk [36].

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CANCER

Maureen Sanderson and Gerson Peltz

OVERVIEW

Cancer is a diverse group of diseases characterized by the uncontrolled growth and spread of abnormal cells. In 2001, cancer was the second leading cause of death in the United States, accounting for 24% of all deaths (National Center for Health Statistics, 2003). In the Lower Rio Grande Valley, the population has lower incidence and mortality rates of breast, prostate, and colorectal cancer—cancers associated with nutrition—than do residents of Texas and the United States, but rates of cervical cancer, which is also associated with nutrition, outpace those of the state and the nation. Current hypotheses of cervical cancer etiology focus on the human papillomavirus and risk factors, including nutrition, that increase or decrease susceptibility to the virus.

Studies of various aspects of nutrition, including energy balance, physical activity, and dietary intake of fat, fruits and vegetables, fiber, and vitamin and mineral supplements, have yielded information about associations between cancer and diet, and findings are briefly reviewed. What follows are descriptions of two new studies under way in the Lower Rio Grande Valley undertaken to better characterize breast cancer in this population and to test primary and secondary culturally sensitive interventions to control cervical cancer. Few studies have focused solely on the effects of dietary factors and cancer risk in a predominantly Hispanic population.

Celebrants of Dia de los Muertos *left beautiful flowers in this Starr County cemetery lovingly tended by married caretakers. Culturally sensitive interventions to reduce cervical cancer risk are under way.*

CANCER IN THE LOWER RIO GRANDE VALLEY

The diverse array of diseases known as cancer is generally thought to be caused by genetic characteristics and a combination of environmental factors, including nutrition. Evidence for the link between nutrition and cancer has been based on *(a)* ecologic studies correlating a country's consumption of specific nutrients with its cancer incidence and *(b)* studies among persons emigrating from countries with low cancer incidence to countries with high cancer incidence. In 1981, Doll and Peto estimated that 35% of cancer deaths could be attributed, in part, to nutrition, a contribution to mortality equal to that of smoking. An international group, the World Cancer Research Fund, reported a similar estimate in 1997; however, this figure may be as low as 10% or as high as 70% (World Cancer Research Fund, 1997), and the specific aspects of the diet associated with cancer are still unclear. In the text below we compare incidence and mortality rates among non-Hispanic whites and Hispanics in the United States, Texas, and the Lower Rio Grande Valley for breast, prostate, colorectal, and cervical cancer (Table 6.7).

Breast Cancer

Breast cancer is the most commonly diagnosed cancer among women in the United States and the second leading cause of cancer deaths. As seen in Figure 6.14, the U.S. 1996–2000 incidence rates for breast cancer were higher among non-Hispanic whites than among Hispanics (Ries et al., 2003). Similarly, in Texas and the Lower Rio Grande Valley, the 1995–1999 breast cancer incidence rates were higher among non-Hispanic whites than among Hispanics (Figure 6.14) (written personal communication with D.

Table 6.7. Cancer Incidence and Mortality Per 100,000—United States, Texas, and Lower Rio Grande Valley, 1996–2000

Cancer	United States		Texas		Lower Rio Grande Valley	
	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic	Non-Hispanic White	Hispanic
Breast Cancer						
Incidence	148.3	89.8	131.3	81.9	144.0	78.9
Mortality	27.4	17.9	23.3	20.2	26.7	21.5
Prostate Cancer						
Incidence	163.3	137.2	157.1	107.2	202.3	114.6
Mortality	30.5	24.1	31.4	23.0	22.4	23.7
Colorectal Cancer						
Incidence	54.8	40.0	52.8	35.8	55.5	30.9
Mortality	20.8	14.3	20.4	14.8	16.1	12.4
Cervical Cancer						
Incidence	7.6	16.8	8.2	17.6	9.9	18.7
Mortality	2.6	3.7	2.7	5.0	2.5	5.8

Risser, epidemiologist, Texas Department of Health, July 28, 2003). Figure 6.15 indicates that the 1996–2000 breast cancer mortality rate in the United States was also higher among non-Hispanic whites than among Hispanics. While the 1995–2001 breast cancer mortality rates among non-Hispanic white women in Texas and Lower Rio Grande Valley were similar to those of non-Hispanic white women in the United States, cancer mortality rates were elevated among Hispanic women compared with the rates for Hispanic women nationwide (Figure 6.15).

The percentage of women diagnosed with advanced stage disease from 1995 to 1999 in the Lower Rio Grande Valley was higher among Hispanics (41.4%) than among non-Hispanic whites (34.4%). Hispanics in the Lower Rio Grande Valley are diagnosed with cancer at a more advanced stage than are non-Hispanic whites, indicating that in the Lower Rio Grande Valley Hispanics are less likely to be screened for breast cancer than are non-Hispanic whites.

Prostate Cancer

Prostate cancer, the most frequently diagnosed cancer among men in the United States, is the second leading cause of cancer deaths. From Figure 6.16, the 1996–2000 prostate cancer incidence rates were higher among non-Hispanic white men than among Hispanic men (Ries et al., 2003). In Texas and the Lower Rio Grande Valley, the 1995–1999 incidence rates of prostate cancer were considerably higher among non-Hispanic whites than among Hispanics (Figure 6.16) (D. Risser, personal communication, July 28, 2003).

Similarly, the U.S. prostate cancer mortality rates for 1996–2000 were higher among non-Hispanic white men than among Hispanic men (Figure 6.17). This pattern was similar for the 1995–2001 prostate cancer mortality rates for Texas non-Hispanic whites and Hispanics; however, in contrast, the prostate cancer mortality rate was slightly higher among Lower Rio Grande Valley Hispanics than non-Hispanic whites (Figure 6.17).

From 1995 to 1999, the percentage of men in the Lower Rio Grande Valley diagnosed with advanced-stage disease was higher among Hispanics (16.9%) than among non-Hispanic whites (13.0%), which may account for a narrowing of the ethnic gap when comparing incidence and mortality. As was the case for breast cancer, screening is less likely to occur among the Hispanic population than among the non-Hispanic white population.

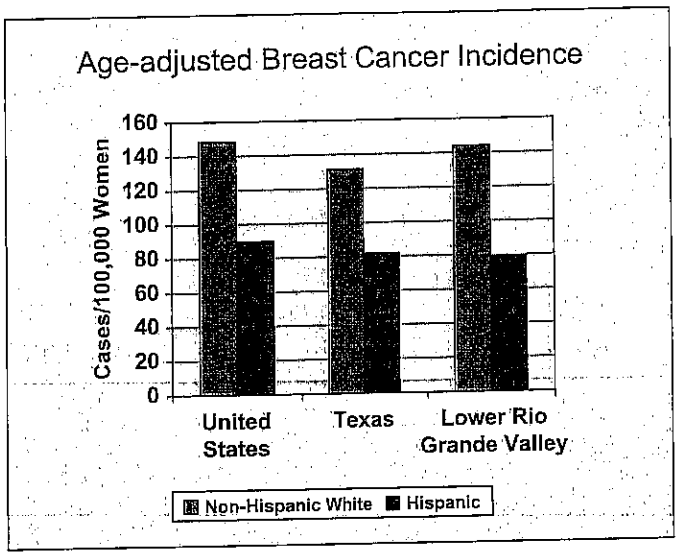

Figure 6.14. *The age-adjusted breast cancer incidence rate is lower in Hispanic women than in non-Hispanic white women in the United States, Texas, and the Lower Rio Grande Valley.*

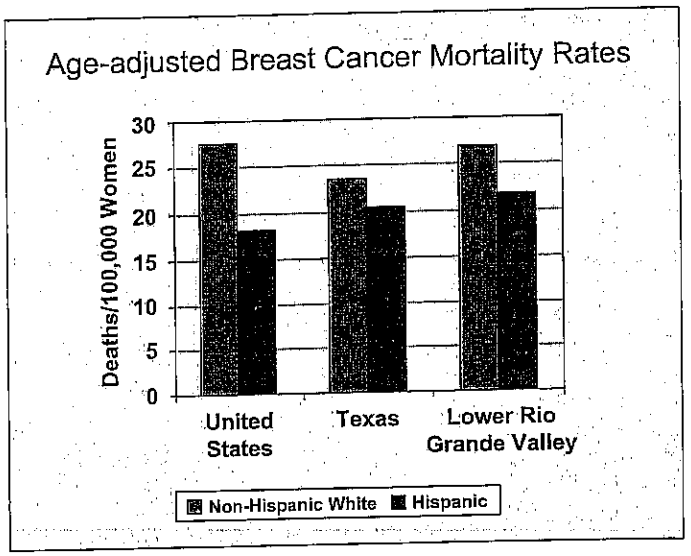

Figure 6.15. *Breast cancer mortality in non-Hispanic white women outpaced that in Hispanic women, but rates were higher among Hispanic women in Texas and the Lower Rio Grande Valley than in the United States.*

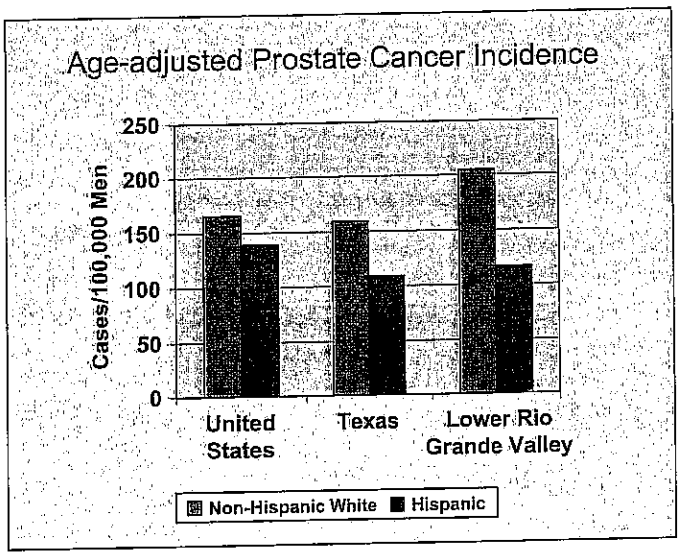

Figure 6.16. *The age-adjusted prostate cancer incidence rate was higher in non-Hispanic white men than in Hispanic men and higher in the Lower Rio Grande Valley than in the United States or Texas. Rates in Hispanic men were highest in the United States overall (137.2/100,000) followed by rates in the Lower Rio Grande Valley (114.6/100,000) and Texas (107.2/100,000).*

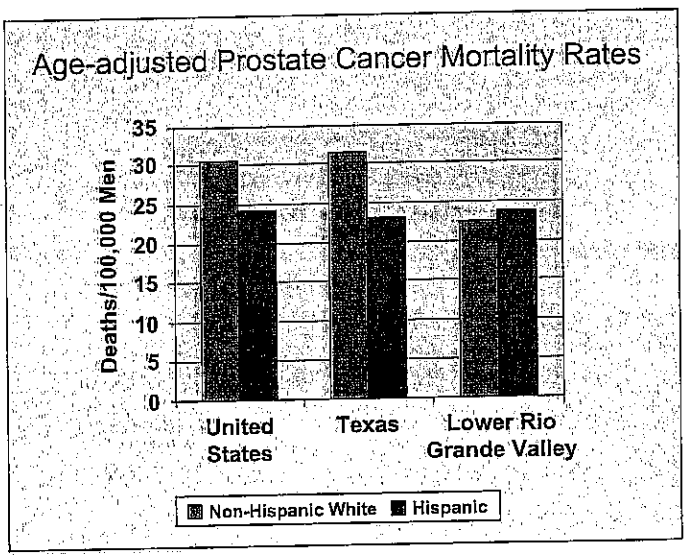

Figure 6.17. *The age-adjusted prostate cancer mortality rate among non-Hispanic white men was lower in the Lower Rio Grande Valley than in Texas and in the United States. Prostate cancer mortality rates in the Lower Rio Grande Valley were slightly higher for Hispanic men than they were for non-Hispanic white men, who were more likely to be screened.*

Colorectal Cancer

Colorectal cancer is the fourth most frequently diagnosed cancer in the U.S. population and is the second leading cause of cancer deaths. As seen in Figure 6.18, the 1996–2000 colorectal cancer incidence rates were higher among non-Hispanic whites than among Hispanics (Ries et al., 2003). In Texas and the Lower Rio Grande Valley, the 1995–1999 incidence rates from colorectal cancer were higher among non-Hispanic whites than among Hispanics (Figure 6.18), and the difference in incidence rates was most

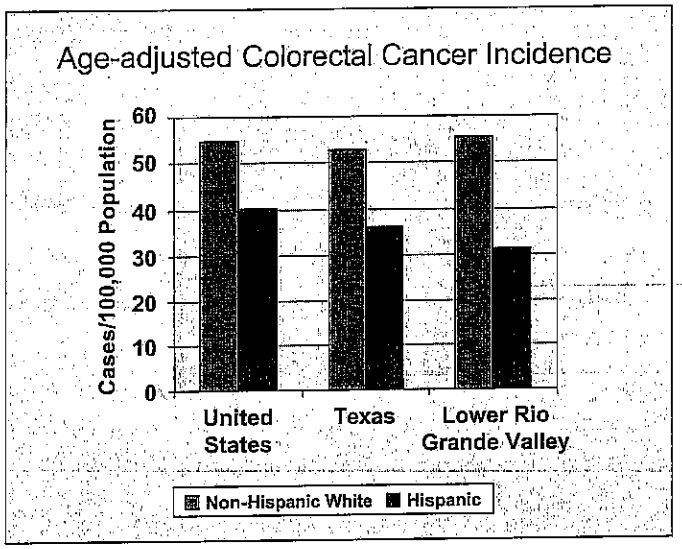

Figure 6.18. *The 1996–2000 rates of new colorectal cancer cases were higher in non-Hispanic whites than in the Hispanic population and somewhat higher in the Lower Rio Grande Valley and in the United States overall than in Texas. The incidence rate in the Hispanic population was lowest in the Lower Rio Grande Valley.*

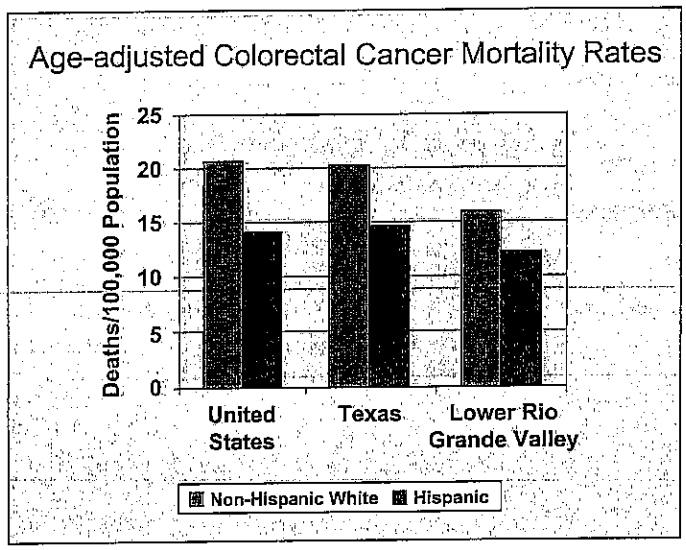

Figure 6.19. *The 1996–2000 deaths from colorectal cancer were higher among non-Hispanic whites in the United States and Texas than in the Lower Rio Grande Valley. The difference between non-Hispanic whites and Hispanics was not as pronounced in the Lower Rio Grande Valley as that between those groups in the United States and in Texas.*

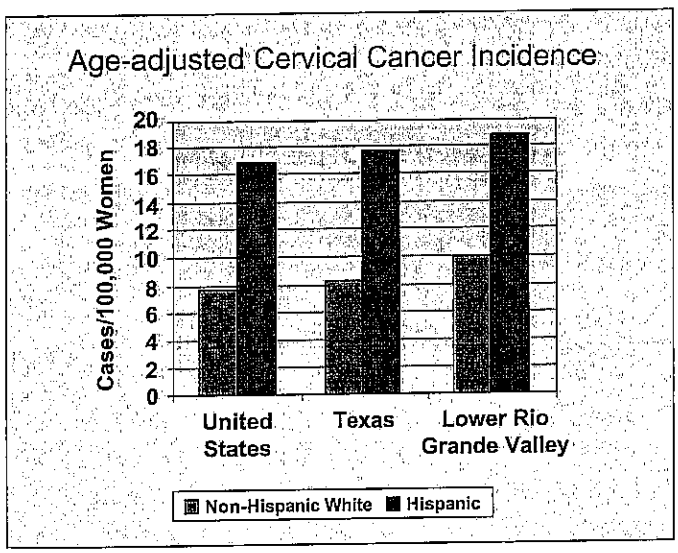

Figure 6.20. *In 1996–2000, cervical cancer incidence rates in Hispanic women were approximately two times higher than rates in non-Hispanic white women. Rates for both non-Hispanic white and Hispanic women were highest in the Lower Rio Grande Valley.*

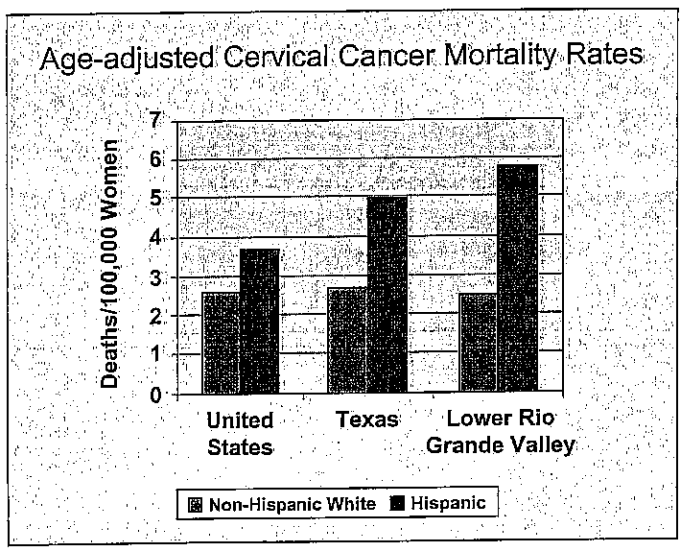

Figure 6.21. *In Hispanic women, the 1996–2000 cervical cancer mortality rates were higher in Texas than in the United States and higher in the Lower Rio Grande Valley than in Texas. In fact, the cervical cancer mortality rate for Hispanic women in the Lower Rio Grande Valley was more than twice that of non-Hispanic white women in the United States.*

dramatic in this pair (25 cases/100,000) (D. Risser, personal communication, July 28, 2003). This was also true for U.S. colorectal cancer mortality rates for 1996–2000 (Figure 6.19). Indeed, the pattern was similar for the 1995–2001 colorectal cancer mortality rates for Texas and Lower Rio Grande Valley non-Hispanic whites and Hispanics (Figure 6.19). But in the percentage of persons diagnosed with advanced-stage disease from 1995 to 1999, the difference narrowed to only 2.1 percentage points: 63.7% for non-Hispanic whites and 61.6% for Hispanics.

Cervical Cancer

The U.S. 1996–2000 cervical cancer incidence rate was higher among Hispanics than among non-Hispanic whites (Ries et al., 2003), and a similar difference was seen for Texas and the Lower Rio Grande Valley 1995–1999; however, the rates were elevated compared with those for the United States (Figure 6.20) (D. Risser, personal communication, July 28, 2003). Across the border, the neighboring nation of Mexico has one of the highest incidence rates of cervical cancer in the world (44.4/100,000) (Parkin, Pisani, & Ferlay, 1999).

In the United States from 1996 to 2000, Hispanic women had a higher mortality rate from cervical cancer than did non-Hispanic white women. In Texas from 1995 to 2001, cervical cancer mortality rates were similar: they were higher among Hispanics than among non-Hispanic whites (Figure 6.21). In the Lower Rio Grande Valley, the mortality rate among Hispanics was more than twice that of non-Hispanic whites (Figure 6.21). The four Lower Rio Grande Valley counties were all among the top 20% of U.S. counties for mortality from cervical cancer between 1970 and 1994 with rates ranging from 5.28 per 100,000 in Hidalgo county to 6.35 per 100,000 in Willacy county (written personal communication from H. P. Freeman, M.D., director, Center to Reduce Cancer Health Disparities, November 28, 2001).

THE ROLE OF NUTRITION

Cancer Etiology Related to Energy Balance

In animal studies, energy restriction resulted in a reduction of mammary and other tumors (Willett & Stampfer, 1986). Energy balance, defined as the difference between energy intake through diet and energy expenditure through physical activity, appears to be driven more by physical activity than by diet (Birt, Kris, Choe, & Pelling, 1992). Height tends to be a marker for childhood and adolescent nutrition, while weight tends to be a marker for adult nutrition. Greater height has been associated with increased breast and colorectal cancer (Hunter & Willet, 1992; Chute et al., 1999). Excess body fat is positively related to colorectal cancer (Giovannucci et al., 1995a) and postmenopausal breast cancer, but negatively related to premenopausal breast cancer (Hunter & Willett, 1993).

Cancer Etiology Related to Dietary Fat

From animal models it appears that dietary fat promotes tumors, but it is unclear whether this effect is independent of energy intake (Willet & Stampfer, 1986). Intake of dietary fat is thought to be associated with breast, prostate, and colorectal cancers because of the large international variation in cancer incidence that coincides with per capita consumption of animal fat (Prentice & Sheppard, 1990). Evidence in clinical studies is mixed for these associations but would appear to be stronger for meat intake, especially for colorectal cancer, than for dietary fat in general (Willett et al., 1990). The proposed biological mechanism for the link between fat intake and colorectal cancer is that dietary fat increases excretion of bile acids, which may act as carcinogens (Giovannucci et al., 1992). Physical activity is associated with reduced risk of colorectal cancer (Colditz, Cannuscio, & Frazier, 1997); thus, it is difficult to disentangle the independent effects of diet and physical activity.

Cancer Prevention Related to Fruits and Vegetables

Greater intake of fruits and vegetables is associated with reduced risk of a number of cancers, including lung (Ziegler, Mayne, & Swanson, 1996), stomach (Kono & Hirohata, 1996), and breast and cervical cancers (Willett & Trichopoulos, 1996). There is an inverse relationship between intake of the carotenoid lycopene and prostate cancer (Giovannucci et al., 1995b). The specific constituents of fruits and vegetables linked to reductions in risk are unknown, but protective factors could include carotenoids, folic acid, vitamin C, flavonoids, phytoestrogens, isothiocyanates, and fiber (Steinmetz & Potter, 1991).

Cancer Prevention Related to Dietary Fiber

A diet high in fiber has been recommended to reduce colorectal cancer risk; however, recent evidence suggests that fruits and vegetables are more effective in protecting against colorectal cancer than grains (Potter, 1996). Several biological mechanisms have been proposed for this association, including binding carcinogens and speeding their transit through the gut (Story & Kritchevsky, 1978).

Cancer Prevention Related to Supplements

Since many cancers are inversely associated with fruit and vegetable intake, several studies have investigated the

effect of high-dose vitamin and mineral supplements, including those containing vitamins C and E, on cancer risk with inconsistent results (Willett, 1999). In a randomized trial of beta-carotene and vitamin A and lung cancer, investigators found risk increased among those who received the supplement (Omenn et al., 1996). Based on animal studies and ecologic studies, selenium is thought to be related to reduced breast and colon cancer (Clark, 1985); however, there is no evidence from human studies (Hunter et al., 1990). There may be a modest protective effect of calcium on colon cancer risk (Hyman et al., 1998). Long-term use of folic acid supplements appears to be effective in reducing colon cancer (White, Shannon, & Patterson, 1997). Such a strategy may be important for persons with a polymorphism of a gene involved in folic acid metabolism known to be related to increased colon cancer risk (Ma et al., 1997).

RECENTLY FUNDED RESEARCH

Two studies proposed by investigators from Houston and Brownsville have recently been funded to investigate breast and cervical cancer. Headed by principal investigators Gerson Peltz, M.D., from The University of Texas at Brownsville and Texas Southmost College and Maureen Sanderson, Ph.D., from The University of Texas School of Public Health, Brownsville Regional Campus, the breast cancer study is a clinic-based case-control study, which includes completion of a questionnaire, anthropometric evaluation, and a blood draw. The investigators, whose work is funded by the U.S. Department of Defense, plan to collect information on dietary intake, including consumption of phytoestrogens, in an attempt to identify factors that protect against breast cancer in this population. In addition, detailed information on body size will be collected and bioelectrical impedance analysis will be utilized to estimate lean body mass and body fat. The primary aim of the cervical cancer grant, which is headed by Sanderson and Guillermo Tortolero-Luna, M.D., Ph.D., at The University of Texas School of Public Health at Houston, is to develop and test culturally sensitive primary and secondary interventions to reduce the burden of cervical cancer in the Lower Rio Grande Valley. Interventions will include those related to diet and physical activity.

SUMMARY

Residents of the Lower Rio Grande Valley have lower incidence and mortality rates of breast, colorectal, and prostate cancer than their counterparts in Texas and the United States, but higher rates of cervical cancer. Nutrition appears to play a role in the etiology and prevention of these cancers. Two studies of cancer prevention focusing on Pap smear screening have been conducted in the Lower Rio Grande Valley (Oleszkowic, Kresch, & Painter, 1995; Ramirez et al., 1999); however, neither of these studies collected information on dietary intake. A federally funded study of breast cancer will collect information on dietary intake and body size in an attempt to identify factors that may protect Hispanic women from breast cancer.

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REPORTS

Insulin-Like Growth Factor-I, Soy Protein Intake, and Breast Cancer Risk

Maureen Sanderson, Xiao Ou Shu, Herbert Yu, Qi Dai, Alecia S. Malin, Yu-Tang Gao, and Wei Zheng

Abstract: *Previous studies have found that estrogen enhances the effect of insulin-like growth factor-I (IGF-I) levels on breast cancer cell growth. Participants in the Shanghai Breast Cancer Study (SBCS) consumed large amounts of soy that was high in isoflavones, which act as weak estrogens and as anti-estrogens. We assessed whether soy protein intake modified the effect of IGF-I levels on breast cancer risk. The SBCS is a population-based case-control study of breast cancer among women aged 25–64 conducted between 1996 and 1998 in urban Shanghai. In-person interviews were completed with 1,459 incident breast cancer cases ascertained through a population-based cancer registry and 1,556 controls randomly selected from the general population (with respective response rates of 91% and 90%). This analysis is restricted to the 397 cases and 397 matched controls for whom information on IGF-I levels was available. For premenopausal breast cancer, we found nearly significant interactions between soy protein intake and IGF-I levels (*P = *0.080) and insulin-like growth factor-binding protein-3 (IGFBP-3) levels (*P = *0.057). The direction of the interaction appeared to be negative for IGF-I levels but was positive for IGFBP-3 levels. No interaction was evident between soy protein intake and IGF-I or IGFBP-3 levels among postmenopausal women. Our results suggest that soy protein intake may negatively modulate the effect of IGF-I and may positively modulate the effect of IGFBP-3 levels on premenopausal breast cancer risk. Further studies are needed to confirm our finding and to understand the biological mechanisms of these potential interactions.*

Introduction

Insulin-like growth factor-I (IGF-I) is thought to play a role in the pathogenesis of breast cancer due to its mitogenic and anti-apoptotic effects on mammary cell lines (1). Insulin-like growth factor-binding protein-3 (IGFBP-3) regulates IGF-I bioactivity by binding to IGF-I (2). Of the nine human studies of IGF-I levels and premenopausal breast cancer (3–11), IGF-I was positively associated in four studies of Caucasian women (3–6) and in the Shanghai Breast Cancer Study (SBCS) of Asian women (7). Seven of these studies also investigated IGFBP-3, with four studies reporting positive associations (3,5–7) and three studies reporting no association (8,9,11). Only one human study, conducted among African-American women (12), of the 12 studies of IGF-I levels and postmenopausal breast cancer (4–7,9–11,13–16) found a positive relation. Similarly, only one study, using the SBCS (7), of the eight studies of IGFBP-3 and breast cancer (5,6,9,11,14–16) reported an elevated risk of postmenopausal breast cancer associated with increased IGFBP-3. In vitro studies have shown that estrogen enhances the effect of IGF-I on breast cancer cell growth (17,18), and thus the association of IGF-I with breast cancer risk may be modified by estrogens. One in vivo study, using the SBCS, investigated whether estrogen modified the effect of IGF-I on breast cancer risk (19). They reported synergistic effects between IGF-I levels and two estrogen-related hormones, estrone and testosterone, on breast cancer risk among women diagnosed premenopausally and postmenopausally.

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High consumption of soy during childhood and adulthood has been hypothesized to be protective against breast cancer. One of several mechanisms proposed for this effect is its richness in isoflavones, which may reduce estrogen activity in the breast by competing as weak estrogens for receptor sites (20). Isoflavones may also reduce estrogen synthesis (21) and increase sex hormone-binding globulin (22). Of the 12 human studies of adult soy intake on breast cancer risk (23–34) only 4 of those conducted among Asian or Asian-American populations, who consume large amounts of soy, have found statistically significant inverse associations (23–26). A recent Japanese cohort study identified significant inverse relations for isoflavones and breast cancer risk, especially among postmenopausal women, but not for soy in general (35). In one of the studies the reduction in breast cancer risk associated with high soy intake was seen among all women (23), whereas two studies were limited to premenopausal women (24,25). A previous report from the SBCS found that high adult soy intake was associated with a reduced risk of breast cancer for women with a higher body mass index (BMI) or with an estrogen receptor/progesterone receptor-positive breast cancer (26).

As indicated in the SBCS, high soy intake appeared to act as a weak estrogen or anti-estrogen only among women with a high BMI (26), IGF-I levels appeared to exert a mitogenic effect on premenopausal breast cancer (7), and estrogen-related hormones and IGF-I levels worked synergistically in the etiology of breast cancer among all women (19). Given that estrogen tends to enhance the action of IGF-I on mammary cell lines (17,19), we hypothesized that high soy protein intake and high IGF-I levels would act synergistically in increasing breast cancer risk. We also hypothesized that there would be a synergistic interaction between high soy protein intake and high IGFBP-3 on breast cancer because IGFBP-3 was positively associated with breast cancer in an earlier SBCS report (7). We collected information from an additional 97 case-control pairs to combine with the 300 case-control pairs from the previous SBCS report (7) to test these hypotheses.

Material and Methods

Detailed methods of this population-based case-control study appeared elsewhere (36). Briefly, all women aged 25–64 yr who were permanent residents of urban Shanghai at the time of diagnosis of first primary invasive breast cancer (August 1996 through March 1998) were eligible for the study. Two senior pathologists histologically confirmed all diagnoses. We used rapid case ascertainment supplemented by the Shanghai Cancer Registry to identify breast cancer cases who had no prior history of cancer. A total of 1,459 breast cancer cases (91.1% of eligible cases) completed a standardized in-person interview. Of potentially eligible cases, 109 refused (6.8%), 17 died prior to the interview (1.1%), and 17 were not located (1.1%).

The Shanghai Resident Registry, a listing of all permanent adult residents of urban Shanghai, was used to randomly select controls. Controls were frequency matched to cases on age (5-yr interval) based on the number of incident breast cancer cases by age group reported to the Shanghai Cancer Registry from 1990 through 1993. Women who did not reside at the registered address at the time of the study were ineligible. A total of 1,556 controls (90.4% of eligible controls) completed a standardized in-person interview. The remaining 166 potentially eligible controls (9.6%) refused participation. Two women died prior to the interview and were excluded.

The study was approved by relevant institutional review boards in Shanghai and the United States. Women were interviewed at hospitals (cases) or at home (cases and controls) by trained interviewers. The subject questionnaire collected information on demographic factors, reproductive and medical histories, family history of cancer, use of oral contraceptives and hormone replacement therapy, diet, physical activity, lifestyle factors, and body size. Adult soy consumption in the previous 5 yr was collected using a 76-item food-frequency questionnaire. Detailed methods of the calculation of soy protein equivalence appears elsewhere (18). Briefly, foods on the questionnaire used to calculate soy protein equivalence based on the Chinese Food Composition Table (37) were tofu, soy milk, fresh soybeans, dried soybeans, soybean sprouts, and other soy products. Weights were applied to these foods to account for the edible portion, the mixture of non-soyfoods, and seasonal variation. The soyfood items were then summed to estimate total soy protein.

After completing the interview, over 80% of women provided fasting blood samples (1,193 cases, 1,310 controls). Detailed methods of blood collection and testing appeared elsewhere (7). Briefly, plasma was separated from samples and stored at –70°C within 6 h of collection. Within the SBCS, a case-control substudy of quantitative biomarkers was conducted utilizing the 397 cases whose fasting blood samples were collected prior to therapy. A total of 397 controls were selected from the pool of controls who provided fasting blood samples. Cases and controls were individually matched on age (within 5 yr), date of blood collection (within 30 days), menopausal status, and, for premenopausal women, menstruation day (within the first 10 days of menstruation during follicular phase or within 3 days of the first 10 days during the follicular or luteal phases). Matched case-control pairs were analyzed in the same batch assay. Plasma IGF-I and IGFBP-3 concentrations were determined with enzyme-linked immunosorbent assay kits available from DSL, Inc. (Webster, TX). Previous studies of IGF-I and IGFBP-3 and cancer have used these methods with good reproducibility (4,38). The intra-assay and interassay precisions measured as coefficients of variation were 1.5–3.4% and 1.5–8.5% for IGF-I and 0.5–1.9% and 1.8–3.9% for IGFBP-3.

χ^2 tests for categorical variables and paired *t*-tests for continuous variables were used to assess differences in known breast cancer risk factors by case-control status. Spearman

correlation coefficients among controls were computed to evaluate whether levels of IGF-I and IGFBP-3 and soy protein intake were correlated. We used conditional logistic regression to estimate the relative risk of breast cancer associated with IGF-I levels, IGFBP-3 levels, and soy protein intake while controlling for confounders (39). Because these variables were skewed we used the decile distributions among controls and assigned the median of each decile a score for the continuous analysis. We used the tertile distribution among controls to categorize IGF-I levels, IGFBP-3 levels, and soy protein intake in the main effects analysis. The referent group for the main effects analysis was women whose IGF-I level, IGFBP-3 level, or soy protein intake was in the lowest tertile. Due to small numbers in some cells, the median distribution among controls was used to categorize IGF-I levels, IGFBP-3 levels, and soy protein intake in the joint effects analysis. In the joint effects analysis, the referent group was women whose IGF-I or IGFBP-3 levels were less than the median and who consumed less than the median of soy protein. Variables were categorized for all women combined and for premenopausal and postmenopausal women separately. Age, education, family history of breast cancer in a first-degree relative, history of fibroadenoma, leisure physical activity in past 10 yr, BMI, waist-to-hip ratio, parity, age at first live birth, age at menarche, oral contraceptive use, hormone replacement therapy use, and total energy intake were assessed as confounders of the associations between IGF-I levels, IGFBP-3 levels, and soy protein intake and breast cancer. Using a 10% change between unadjusted and adjusted odds ratios (ORs) as evidence of confounding, analyses were adjusted for leisure physical activity in the past 10 yr, parity, and age at first live birth.

Analyses are presented for all women and separately by menopausal status because the effect of some hormonal and growth factor exposures on breast cancer risk is thought to differ by menopausal status. In multiple logistic regression models, we assessed linear trend by treating categorical variables as continuous variables. Interaction terms between IGF-I or IGFBP-3 levels and soy protein intake were included in logistic regression models, and likelihood ratio tests were conducted to examine whether there was evidence of effect modification. We performed an ad hoc analysis that did not involve statistical testing to explore the direction of the effect modification. The OR for the group with high levels of IGF-I or IGFBP-3 and high soy protein intake was divided by the OR for the group with low levels of IGF-I or IGFBP-3 and high soy protein intake. This ratio of ORs was compared with the stratum-specific OR for high levels of IGF-I or IGFBP-3 levels and low soy protein intake.

Results

Table 1 compares known breast cancer risk factors of cases and controls. Compared with controls breast cancer cases were more likely to have a history of fibroadenoma, to have a higher BMI, and to have a later age at first birth and were less likely to have engaged in leisure physical activity in

Table 1. Comparison of Cases and Controls for Selected Risk Factors[a]

	Cases (n = 397)[b]	Controls (n = 397)[b]	P Value
Age	47.8 ± 7.8	47.6 ± 7.9	0.20
Education (%)			
No formal education + elementary school	12.6	14.6	
Middle school	44.3	43.1	
High school	30.5	31.5	
Profession, college, and above	12.6	10.8	0.74
Breast cancer in first-degree relatives (%)	3.0	1.5	0.15
Ever had breast fibroadenoma (%)	9.1	4.8	0.02
Leisure physical activity in past 10 yr (%)	20.9	29.7	<0.01
Body mass index	23.5 ± 3.3	22.9 ± 3.2	0.02
Waist-to-hip ratio	0.80 ± 0.1	0.80 ± 0.1	0.20
Nulliparous (%)	4.0	3.3	0.57
Age at first live birth (yr)[c]	26.9 ± 4.1	26.3 ± 3.9	<0.01
Menarcheal age (yr)	14.7 ± 1.7	14.9 ± 1.7	0.11
Oral contraceptive use (%)	21.9	25.4	0.24
Hormone replacement therapy use (%)	3.5	3.0	0.68
Postmenopausal (%)	36.9	36.4	0.88
Menopausal age (yr)[d]	48.5 ± 4.5	47.8 ± 4.5	0.12
Usual total energy intake (kcal/day)	1,905.7 ± 470.3	1,862.3 ± 481.9	0.16
Soy protein intake (g/day)	11.5 ± 10.8	12.0 ± 9.8	0.53
IGF-I level (ng/ml)[e]	150.6 (144.5–156.9)	138.5 (133.5–143.8)	<0.01
IGFBP-3 level (ng/ml)[e]	3,963.9 (3,813.6–4,119.5)	3,718.2 (3,586.5–3,854.8)	<0.01

a: Subjects with missing values were excluded from the analysis.
b: Unless otherwise specified, mean ± SD is presented.
c: Among women who had live births.
d: Among women with natural menopause.
e: Geometric mean and 95% confidence interval.

the past 10 yr. Mean soy protein intake did not differ significantly between cases and controls, but women with breast cancer had significantly higher levels of IGF-I and IGFBP-3 than did control women. In comparison with the larger study, cases in the substudy had a significantly smaller waist-to-hip ratio (0.80 vs. 0.81) and older age at menarche (14.7 vs. 14.3), whereas controls in the substudy were more likely to be physically active (29.7% vs. 23.7%) and had an older menarcheal age (14.9 vs. 14.7) (data not shown).

Table 2 shows the Spearman correlation coefficients for IGF-I and IGFBP-3 levels and soy protein intake. The correlation between IGF-I and IGFBP-3 levels in this study was not significant among all controls or by menopausal status nor was there a significant correlation between IGF-I levels and soy protein intake among any control subjects. Although the correlation between IGFBP-3 and soy protein intake was not correlated among all controls, there was a significant negative correlation among premenopausal (r = –0.1389; P = 0.03) and significant positive correlation among postmenopausal controls (r = 0.2123; P = 0.01).

Table 3 presents the ORs and 95% confidence intervals (CIs) for breast cancer associated with IGF-I levels, IGFBP-3 levels, and soy protein intake among all women and by menopausal status. There was an indication of significant associations in the continuous analyses of IGF-I or IGFBP-3 among all women. In addition, there were significant trends of increasing risk associated with increasing levels of IGF-I and IGFBP-3 among all women and by menopausal status. The highest tertile of IGF-I was associated with a twofold increase in breast cancer risk (OR = 2.2; 95% CI = 1.4–3.4) that was seen primarily among women who were diagnosed postmenopausally (OR = 2.2; 95% CI = 0.8–5.8). This pattern held for IGFBP-3 (all women OR = 2.6; 95% CI = 1.5–4.5; postmenopausal women OR = 8.1; 95% CI =

Table 2. Correlations Among IGF-I Levels, IGFBP-3 Levels, and Soy Protein Intake Among All Controls and by Menopausal Status

	Spearman Correlation Coefficient (P Value)		
	IGF-I	IGFBP-3	Soy Protein
All controls			
IGF-I	1.00	–0.0829 (0.10)	–0.0043 (0.93)
Soy protein		–0.0036 (0.94)	1.00
Premenopausal controls			
IGF-I	1.00	0.0240 (0.70)	0.0677 (0.28)
Soy protein		–0.1389 (0.03)	1.00
Postmenopausal controls			
IGF-I	1.00	0.0608 (0.47)	–0.0197 (0.82)
Soy protein		0.2123 (0.01)	1.00

Table 3. Odds Ratios of Breast Cancer Associated With Main Effects of IGF-I Levels, IGFBP-3 Levels, and Soy Protein Intake Among All Women and by Menopausal Status

	OR (95% CI)[a]		
	All Women (397 cases, 397 controls)	Premenopausal Women (250 cases, 252 controls)	Postmenopausal Women (147 cases, 145 controls)
IGF-I levels (ng/ml)			
Continuous	1.1 (1.1–1.2)	1.1 (1.0–1.2)	1.2 (1.0–1.3)
Categorical[b]			
Tertile 1	1.0 (referent)	1.0 (referent)	1.0 (referent)
Tertile 2	1.4 (0.9–2.1)	1.1 (0.6–2.0)	1.1 (0.5–2.6)
Tertile 3	2.2 (1.4–3.4)	1.7 (0.9–3.2)	2.2 (0.8–5.8)
P for trend	<0.001	0.003	0.017
IGFBP-3 levels (ng/ml)			
Continuous	1.2 (1.1–1.3)	1.2 (1.1–1.4)	1.2 (1.0–1.4)
Categorical[c]			
Tertile 1	1.0 (referent)	1.0 (referent)	1.0 (referent)
Tertile 2	1.3 (0.8–2.1)	1.8 (1.0–3.4)	0.5 (0.2–1.3)
Tertile 3	2.6 (1.5–4.5)	1.6 (0.9–2.9)	8.1 (2.5–26.0)
P for trend	<0.001	0.002	0.015
Soy protein (g/day)			
Continuous	1.0 (0.9–1.0)	1.0 (0.9–1.1)	1.0 (0.9–1.1)
Categorical[d]			
Tertile 1	1.0 (referent)	1.0 (referent)	1.0 (referent)
Tertile 2	1.0 (0.7–1.4)	0.9 (0.6–1.4)	1.2 (0.7–2.4)
Tertile 3	1.0 (0.7–1.5)	1.1 (0.7–1.6)	0.7 (0.4–1.5)
P for trend	0.455	0.8	0.485

a: Adjusted for leisure physical activity in past 10 yr, parity, and age at first live birth.

b: Tertiles 1–3 for IGF-I levels for all women were <117.7, 117.7–168.3, and ≥168.4; for premenopausal women were <135.9, 135.9–182.4, and ≥182.5; for postmenopausal women were <96.25, 96.25–130.1, and ≥130.2.

c: Tertiles 1–3 for IGFBP-3 levels for all women were <3,306, 3,306–4,190, and ≥4,191; for premenopausal women were <3,086, 3,086–4,003, and ≥4,004; for postmenopausal women were <3,698, 3,698–4,461, and ≥4,462.

d: Tertiles 1–3 for soy protein intake for all women were <6.96, 6.96–12.21, and ≥12.22; for premenopausal women were <6.89, 6.89–11.85, and ≥11.86; for postmenopausal women were <7.28, 7.28–13.18, and ≥13.19.

2.5–26.0). Soy protein intake was not associated with breast cancer risk. Additional adjustment of the IGF-I analysis for IGFBP-3 and the IGFBP-3 analysis for IGF-I weakened most of these associations (data not shown).

Table 4 shows the effect of increasing IGF-I or IGFBP-3 levels on breast cancer risk for women with low and high levels of soy protein intake among all women and by menopausal status. There were borderline significant associations for the continuous analysis of IGF-I and IGFBP-3 levels among all women regardless of level of soy protein intake. In the categorical analysis, high IGF-I level was associated with an increased risk of breast cancer among all women who consumed high levels of soy protein (OR = 1.7; 95% CI = 1.1–2.6). There were twofold elevations in risk associated

Table 4. Odds Ratios of Breast Cancer Associated With Joint Effects of IGF-I or IGFBP-3 Levels and Soy Protein Intake Among All Women and by Menopausal Status

	OR (95% CI)[a]	
	<9.5 g/day Soy Protein (median)	≥9.5 g/day Soy Protein (median)
All women (397 cases, 397 controls)		
IGF-I levels (ng/ml)		
Continuous	1.1 (1.0–1.2)	1.1 (1.0–1.3)
P for interaction	0.863	0.157
Categorical		
<141.0	1.0 (referent)	0.9 (0.6–1.4)
≥141.0	1.6 (1.0–2.5)	1.7 (1.1–2.6)
P for interaction		0.105
IGFBP-3 levels (ng/ml)		
Continuous	1.2 (1.0–1.4)	1.3 (1.0–4.5)
P for interaction	0.663	0.112
Categorical		
<3741.0	1.0 (referent)	0.9 (0.6–1.4)
<3741.0	2.2 (1.3–3.7)	2.3 (1.4–3.8)
P for interaction		0.265
	<9.1 g/day Soy Protein (median)	≥9.1 g/day Soy Protein (median)
Premenopausal women (250 cases, 252 controls)		
IGF-I levels (ng/ml)		
Continuous	1.1 (0.9–1.3)	1.1 (1.0–1.3)
P for interaction	0.393	0.517
Categorical		
<162.6	1.0 (referent)	1.1 (0.6–2.0)
≥162.6	1.6 (0.9–2.8)	1.7 (1.0–2.9)
P for interaction		0.080
IGFBP-3 levels (ng/ml)		
Continuous	1.4 (1.0–1.9)	1.2 (1.0–1.5)
P for interaction	0.297	0.292
Categorical		
<3,526.0	1.0 (referent)	1.1 (0.6–1.8)
≥3526.0	2.1 (1.0–4.3)	2.5 (1.3–5.0)
P for interaction		0.057
	<10.0 g/day Soy Protein (median)	≥10.0 g/day Soy Protein (median)
Postmenopausal women (147 cases, 145 controls)		
IGF-I levels (ng/ml)		
Continuous	1.1 (0.9–1.5)	1.3 (1.0–1.6)
P for interaction	0.689	0.111
Categorical		
<108.3	1.0 (referent)	0.7 (0.3–1.5)
≥108.3	1.5 (0.7–3.2)	1.5 (0.7–3.3)
P for interaction		0.823
IGFBP-3 levels (ng/ml)		
Continuous	1.2 (0.9–1.6)	1.5 (1.0–2.2)
P for interaction	0.689	0.110
Categorical		
<4,060.5	1.0 (referent)	0.9 (0.4–2.1)
≥4,060.5	2.0 (0.9–4.7)	1.4 (0.7–3.2)
P for interaction		0.176

a: Adjusted for leisure physical activity in past 10 yr, parity, and age at first live birth.

with high IGFBP-3 levels among all women and among premenopausal women regardless of amount of soy protein consumed. Although not significantly different, the OR for high IGFBP-3 levels was higher among premenopausal women with high soy protein intake than among premenopausal women with low soy protein intake, whereas the reverse was true for postmenopausal women. Most of these relations were weakened after additional adjustment for IGFBP-3 or IGF-I levels (data not shown).

The *P* values for interaction for IGF-I and IGFBP-3 levels and soy protein intake in the categorical analysis were nearly significant among premenopausal women (IGF-I $P = 0.08$; IGFBP-3 $P = 0.57$) but not among postmenopausal women. Among premenopausal women, the direction of the interaction for IGF-I levels was unclear (OR = 1.6; ratio of ORs = 1.6) but appeared to be positive for IGFBP-3 levels (OR = 2.1; ratio of ORs = 2.3). Although there was no evidence of statistical effect modification, the OR and ratio of ORs differed somewhat among postmenopausal women for IGF-I (OR=1.5; ratio of ORs = 2.1) and IGFBP-3 (OR = 2.0; ratio of ORs = 1.6).

Discussion

We found a nearly significant interaction between high soy protein intake and high IGF-I level and breast cancer risk among premenopausal women. The direction of this interaction was unclear, but the negative correlation between IGF-I level and soy protein intake among premenopausal controls would lead one to believe it was negative. This nonsignificant negative interaction was unexpected but could be due to soy inhibiting tumor cell growth stimulated by growth factors. Genistein, the most common isoflavone, has been shown to inhibit the proliferation of breast cancer cells stimulated by epidermal growth factor (40). In contrast, epidermal growth factor and IGF-I have been shown to act synergistically to stimulate breast cancer cell growth (41). Although not significant, the OR and ratio of ORs for IGF-I level and soy protein intake among postmenopausal women were strikingly different and appeared to be positive rather than negative. The mechanism of this potential positive interaction is unknown but could be related to soy's competition as a weak estrogen for receptor sites (20) or to soy acting as an anti-estrogen by reducing estrogen synthesis (21) and increasing sex hormone-binding globulin (22). A previous analysis of the SBCS identified synergistic effects between IGF-I levels and two estrogen-related hormones, estrone and testosterone, on breast cancer risk among women diagnosed premenopausally and postmenopausally (19).

For IGFBP-3 levels, there was a nearly significant positive interaction among premenopausal women. In contrast, the OR and ratio of ORs among postmenopausal women appeared to suggest a negative interaction. The SBCS is one of two studies that identified a stronger association for premenopausal breast cancer with IGFBP-3 levels than with IGF-I levels (6,7). Thus, the nearly significant positive interaction among premenopausal women was expected, but the nonsignificant negative interaction among postmenopausal women was not. The lack of significant correlations between these IGF-I and IGFBP-3 levels among premenopausal or postmenopausal controls suggests that the biological mechanisms may have differed by menopausal status.

An alternative explanation for soy enhancing the effect of IGF-I levels on breast cancer is that soy may indirectly affect IGF-I levels because estrogens regulate the expression of IGF-I (42), and selective estrogen receptor modulators such as tamoxifen reduce IGF-I levels (43). To determine whether soy was a confounder or intermediate of breast cancer risk, we assessed the correlation between soy protein intake and IGF-I or IGFBP-3 levels. Soy protein intake was not correlated with IGF-I among any control subjects, but IGFBP-3 was correlated among premenopausal and postmenopausal controls. Nagata et al. (44) did not find a significant correlation between soy and IGF-I or IGFBP-3 levels among premenopausal Japanese women; however, to our knowledge no other studies have assessed these correlations among postmenopausal women. In addition, we found no evidence of confounding after adjusting the IGF-I and IGFBP-3 main effect analyses for soy protein intake. This argues against soy being a confounder or in the causal pathway between IGF-I levels and breast cancer risk but does not rule out this possibility for IGFBP-3.

The nonsignificant positive interaction for IGF-I level and soy protein intake among postmenopausal women, indicating that soy protein may act as a weak estrogen or as an anti-estrogen, is in agreement with laboratory studies showing that estrogen enhanced the effect of IGF-I on breast cancer cell growth (17,18). The nearly significant negative interaction between IGF-I level and soy protein intake among premenopausal women could not be explained by the estrogen–IGF-I hypothesis. In our data, we found that soy protein intake was correlated with estrone sulfate ($r = 0.16$; $P = 0.04$) and sex hormone-binding globulin ($r = –0.14$; $P = 0.07$) levels among premenopausal controls and with testosterone ($r = 0.16$; $P = 0.08$) levels among postmenopausal controls. Soy protein intake was not correlated with any other hormones (dehydroepiandrosterone sulfate, estradiol, estrone, or progesterone), suggesting that the soy protein intake among the study population may not be high enough to alter the estrogen level. More studies are needed to better understand the combined effect of estrogen and growth factor on breast cancer.

This study was not without limitations. Data on IGF-I and IGFBP-3 levels were available for a subgroup of women, reducing statistical power to detect effect modification. IGF-I and IGFBP-3 levels among healthy women in our population were lower than those among Caucasian women in the Nurses' Health Study (4), somewhat limiting the generalizability of our results. A potential explanation for these lower levels is the smaller body size and increased physical activity of Asian women compared with American women. Although blood was collected from cases prior to therapy, there may have been an effect of the disease itself on IGF-I and IGFBP-3 levels. Re-

porting of soy intake is prone to misclassification. A recently completed dietary validation study showed that the correlation of soy protein intake derived from the food-frequency questionnaire that we used in the study and the mean of multiple 24-h dietary recalls was 0.49 (45). Misclassification in assessing soy intake may have compromised our ability to investigate the interactive effects of soy protein intake and IGF-I and IGFBP-3 levels. Change of dietary habits over time, particularly after cancer diagnosis, is another concern. A supplementary questionnaire completed by 295 of 397 controls in the present study indicated that soy consumption reported in the last week was highly correlated with soy consumption reported in the past 5 yr ($r = 0.28$; $P < 0.0001$). Main effects and joint effects analyses comparing women whose diets had not changed with all women were slightly more pronounced but fairly comparable.

Although in vitro (17,18) and in vivo (19) studies of breast cancer have investigated the interaction between estrogen and IGF-I levels, ours is the first in vivo study to investigate the interaction between soy protein, a weak estrogen and anti-estrogen, and IGF-I levels. The relatively high soy consumption among our population compared with the rest of the world made this analysis possible. Additional strengths of this study are its population-based nature and high response rates among subjects (cases: 91%; controls: 90%), which minimizes selection bias. We adjusted for known breast cancer risk factors and evaluated the IGF-I levels, IGFBP-3 levels, and soy protein intake and breast cancer associations in conjunction with menopausal status, a suspected effect modifier of these relations. We also assessed BMI, waist-to-hip ratio, and use of hormone replacement therapy as effect modifiers of the IGF-I–breast cancer association with no evidence of such (data not shown). With the exception of waist-to-hip ratio, age at menarche, and physical activity, we were successful in selecting women for this substudy who were comparable with women from the larger study.

In summary, our results suggest that soy protein intake may modify the effect of IGF-I and IGFPB-3 levels on premenopausal breast cancer risk. Further studies with larger sample sizes are needed to confirm our finding and to understand the biological mechanism of these potential interactions. Should these interactions persist in other studies, intervention studies using soy protein must account for womens' IGF-I and IGFBP-3 levels in their design.

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Grant Abstract

DETERMINANTS OF BREAST CANCER RISK IN LATINA GIRLS

A. STATEMENT OF HYPOTHESIS AND SPECIFIC AIMS

The Research Plan describes a two-part study. Phase one will involve the development of a dietary acculturation scale instrument that measures factors associated with the dietary acculturation process for Latino families who live in a specific region of the Lower Rio Grande Valley in Texas. Phase two will involve: a) exploring associations between maternal dietary acculturation level and specific dietary behaviors in 4th grade Latina girls and b) exploring associations between specific dietary behaviors and physiological breast cancer risk factors in 4th grade Latina girls. The hypothesis that will be tested is: Latina girls who have a higher total energy intake and a higher % of calories from fat and saturated fat will have a greater body mass index (BMI) compared to Latina girls with a lower total energy intake and % calories from fat and saturated fat.

Phase One -

Specific Aim 1: To develop a dietary scale instrument that measures factors associated with the dietary acculturation process for Latino families who live in a specific region of the Lower Rio Grande Valley.

Phase Two -

Specific Aim 2: To explore associations between maternal dietary acculturation level and specific dietary behaviors in 4th grade Mexican American girls in 4th grade Latina girls.

Specific Aim 3: To explore associations between specific dietary behaviors and physiological breast cancer risk factors in 4th grade Latina girls including:

A. obesity (body mass index) and abdominal obesity
B. plasma insulin, plasma glucose, and serum c-peptide
C. plasma insulin-like growth factor-1 (IGF-1) levels, plasma insulin-like growth factor binding protein-3 (IGFBP-3) levels, serum estradiol (E2) and serum sex-hormone binding globulin (SHBG)

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1) Running head: Risk Behaviors by Ethnicity and Border Residence

2) Title: **Risk Behaviors by Ethnicity and Texas-Mexico Border Residence**

3) Authors: Maureen Sanderson, Ph.D., Maria E. Fernandez, Ph.D., Ronald J. Dutton, Ph.D., Arlette Ponder, M.A.H.S., Dina Sosa, B.S., Gerson Peltz, M.D.

4) **Abstract:**

Objective: To determine whether residence on the Texas-Mexico border would modify the effect of ethnic differences on risk behaviors.

Design: We performed an analysis of 1999-2003 cross-sectional data from the Texas Behavioral Risk Factor Surveillance System (BRFSS).

Setting: 15 Texas-Mexico border counties compared with 239 Texas non-border counties.

Participants: 521 white and 1,722 Hispanic residents of Texas-Mexico border counties and 16,904 white and 4,933 Hispanic residents of Texas non-border counties.

Main Outcome Measures: Health risk behaviors including overweight, obesity, physical inactivity, fruit or vegetable consumption, heavy drinking, binge drinking and smoking.

Results: Hispanic women and men were more likely to be overweight, obese, and physically inactive, and less likely to consumer fewer than 5 fruits or vegetables per day than whites regardless of residence. Ethnic differences in heavy and binge drinking differed by residence and gender. After adjustment for age, educational level, annual household income, perceived general health and diabetes, most behaviors that were higher or lower remained significant among non-border residents, but were no longer significant among border residents.

Conclusions: The only evidence of effect modification was binge drinking among males and most associations were weaker among border residents than among non-border residents.

5) Keywords: Risk behaviors, Ethnicity, Texas-Mexico border

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Introduction

The prevalence of conditions and behaviors that place persons at risk of chronic disease differs by ethnicity. Myers et al. (1) conducted a review of existing literature in 1995 of behavioral risk factors by ethnic group in comparison with white (non-Hispanics) henceforth referred to as white. As indicated in the review there was substantial evidence of obesity among female African Americans, Hispanics and Native Americans and strong evidence of obesity among Pacific Islanders. Among African American females and males over age 40, Asians/Pacific Islanders, and Hispanic females there was some evidence of no regular exercise. With regard to poor diet, defined as excess intake of dietary fat and inadequate intake of dietary fiber, there was strong evidence among female African Americans, and some evidence among Asians/Pacific Islanders, Hispanics and Native Americans. There was strong evidence of heavy drinking, defined as consuming more than two alcoholic drinks per day, among African Americans and Native Americans, and some evidence among Southeast Asian males and Hispanic males. There was strong evidence of higher smoking rates among African American males over age 40, immigrant Asian/Pacific Islander males, Hispanic males and Native American males; however, there was strong evidence of lower smoking rates among Hispanic females. Using data from the 2001-2002 Behavioral Risk Factor Surveillance System (BRFSS), Denny et al. (2) reported that American Indians/Alaska Natives had higher prevalence of obesity, physical inactivity and smoking than whites.

Winkleby et al. (3) posited that lower socioeconomic status may be a possible explanation for ethnic disparities in risk behaviors. In subsequent studies utilizing data from the National Health and Nutrition Examination Survey III, Winkleby et al. found higher prevalence

of obesity and physical inactivity in African American and Hispanic women (4) and smoking in African American men (5) compared to whites less than age 65 after adjustment for age and educational level or family income. Winkleby and Cubbin (6) assessed changes in health behaviors from 1990 to 2000 by ethnicity, gender and age using national BRFSS data. After adjusting 2000 data for educational attainment and annual household income, they found ethnic differences in various age groups (18-24 years, 25-44 years, 54-64 years, 64-74 years) for obesity, sedentary behavior, low vegetable or fruit intake, and smoking.

Few previous studies have investigated the proximity to the US-Mexico border as a community-level measure of socioeconomic status. The US-Mexico border region is one of the poorest in the United States (US). In 2000, it was the location of 6 of the 10 metropolitan areas with the lowest per capita income and the 3 poorest metropolitan areas were located on the Texas-Mexico border (7). Using BRFSS data, Coughlin et al. (8) found that Hispanic women in US-Mexico border counties were less likely to have had a recent mammogram or Pap test than white women in border counties, and Hispanic and white women in non-border counties. In a study of elderly Mexican Americans, Patel et al. (9) reported that the effect of neighborhood disadvantage on poorer self-rated health was two to three times higher among persons living within 50 miles of the US-Mexico border than among other persons. The purpose of the present study was to determine whether residence on the Texas-Mexico border would modify the effect of ethnic differences on risk behaviors. We used data from the BRFSS conducted statewide in Texas to investigate our hypothesis that ethnic differences would be more striking among border residents than among non-border residents.

Methods

Each year approximately 5000 to 6000 Texas residents complete the cross-sectional statewide BRFSS (10). Random digit dialing is used to select adults 18 years of age or older who live in a private household to complete a telephone interview. Questions are taken from the Centers for Disease Control and Prevention BRFSS and cover risk behaviors that contribute to morbidity and mortality (11). Although the BRFSS does not break down Hispanic ethnicity into its component parts; 76% of Hispanics in Texas are of Mexican origin (12), therefore Hispanics in the Texas BRFSS are predominantly Mexican American. For most risk behaviors we used the combined 1999-2003 Texas BRFSS consisting of approximately 5,613 adults annually reflecting approximately 15.2 million persons residing in the 254 counties in the state. We excluded persons of ethnicities other than white or Hispanic (n=3,688) and those with missing information on place of residence (n=298) resulting in 24,080 adults for this analysis. Border residence was for the 15 counties contiguous with the Mexico border and non-border residence was for the remaining 239 counties. Response rates to the Texas BRFSS were 36.2% in 1999, 33.5% in 2000, 39.7% in 2001, 46.2% in 2002, and 41.2% in 2003.

Self-reported weight and height were used to calculate body mass index (BMI = weight in kilograms/height in meters^2). Overweight was defined as a BMI of 25 or greater and obese was defined as a BMI of 30 or greater (obese is a subset of overweight). Physical inactivity was no leisure-time physical activity in the past month. To calculate fruit or vegetable consumption respondents were asked how many servings of six different fruits and vegetables (fruit juices, fruit, green salad, potatoes, carrots and other vegetables) they usually consumed per day, week, month or year and consumption of fewer than 5 servings per day was considered a risk factor.

Heavy drinking was defined differently for men and women: averaging 2 or more alcoholic beverages on a daily basis for men and averaging 1 or more alcoholic beverage on a daily basis for women during the past month (11). Binge drinking was having five or more alcoholic beverages on one or more occasions in the past month. Smoking was defined as having smoked at least 100 cigarettes and engaging in current smoking.

Probability sample weights were applied to the sample to reflect the population of non-border and border residents for each year of the survey. Weights were derived by multiplying factors accounting for the probability of selection within strata (subsets of area code/prefix combinations), the number of adults in the household, and the number of phones in the household by a post-stratification weight reflecting the age and sex distribution of Texas' adult population (ages 18 years and older). The post-stratification weight adjusts for non-coverage and non-response. Data were analyzed using Survey Data Analysis (SUDAAN) to account for sampling within strata and multiple years of data (13). Unconditional logistic regression was used to assess the association between ethnicity and risk behaviors while controlling for confounding (14). An interaction term between ethnicity and border residence was included in logistic regression models and likelihood ratio tests were performed to examine effect modification. Although the only behavior to exhibit effect modification was binge drinking among males (p-value for interaction=0.03) we present analyses stratified by border residence for ease of interpretation. We added all theoretically relevant variables as defined in Table 1 as potential confounders including age, educational level, annual household income, perceived general health and diabetes. These variables were selected because they address socioeconomic status, perceived health status and morbidity which may impact risk behaviors. We also stratified by gender since the effect of ethnicity on risk behaviors appears to differ by gender.

Results

The distribution of potential confounding factors by ethnicity, residence, and gender is presented in table 1. In comparison to whites, Hispanics tended to be younger, to be less educated, to have a lower annual household income, and to rate their general health as poor or fair regardless of residence or gender. The prevalence of diabetes was higher among Hispanic than white non-border females, while the reverse was true among border males.

Table 2 shows the prevalence of risk behaviors by ethnicity, residence, and gender. Hispanics of both genders and residences were more likely to be overweight, obese, physically inactive, and consume fewer than 5 fruits or vegetables per day than whites. Hispanic females were less likely to engage in heavy drinking and smoking than white females, but there was little difference in the prevalence of binge drinking comparing Hispanic and white females regardless of residence. In comparison with white males, Hispanic males were more likely to drink heavily, to binge drink and to smoke than whites regardless of residence.

Table 3 presents the unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for risk behaviors associated with ethnicity and residence among women and men, respectively. Adjustment weakened most associations, strengthened some associations (smoking in women and overweight in men), and reversed some associations (consumption of fewer than 5 fruits or vegetables per day, heavy drinking in border women, binge drinking in border men, and smoking in men). With the exception of physical inactivity in border males, Hispanics of both genders were more likely than whites to be overweight, obese and physically inactive than whites. In contrast, Hispanics were less likely than whites to consume fewer than 5 fruits or vegetables per day and to smoke. After adjustment these findings were significant among non-

border residents but not among border residents. The findings for heavy and binge drinking were mixed by residence and gender. Although the p-value for interaction was not significant for heavy drinking among females (p=0.49) the odds ratios are on either side of the null-value of 1.0 indicating Hispanic women who did not live on the border were less likely to drink heavily than white women, while Hispanic women who did live on the border were more likely to drink heavily than white women. The opposite pattern was seen for binge drinking in men (p-value for interaction=0.03) with non-border Hispanics more likely to binge drink than whites and border Hispanic less likely to drink than whites. Hispanic women were less likely to binge drink than white women regardless of residence, and there was little difference in heavy drinking by ethnicity or residence among men.

Discussion

Our findings of higher rates of overweight and obesity among Hispanics of both genders than among whites regardless of border residence are comparable to several studies. The Stanford Five-City Project reported higher mean values of BMI among Mexican Americans overall (15), the San Antonio Heart Study reported higher mean values of BMI among Mexican Americans of both genders (16), and an analysis of the NHANES III reported higher mean values of BMI among Mexican American females (4) than their white counterparts. The New York City BRFSS defined overweight as greater than 110% ideal Metropolitan relative weight and obesity as greater than 120% of ideal weight (17). They found elevations in overweight and obesity among Hispanic females relative to white females, but not among males. In an analysis of changes in health behaviors between 1990 and 2000 using national BRFSS data, Winkleby and Cubbin (6) found higher prevalences of obesity among Hispanics than among whites however the differences appeared to be narrowing between 1990 and 2000. With the exception of obesity among men, our study found smaller differences among border than non-border residents for overweight and obesity which may reflect a narrowing of the white-Hispanic gap on the border that is not evident in the non-border region.

We saw higher levels of physical inactivity among Hispanics relative to whites, limited to non-border males, which is similar to the findings of most other studies. A modified BRFSS telephone survey conducted in San Francisco reported significantly higher levels of no leisure-time physical activity among Latinos of both genders compared to whites (18). Burchfiel et al. (19) completed personal interviews as part of the San Luis Valley Diabetes Study and reported higher levels of physical inactivity, defined as work-related, among Hispanics of both genders

compared to Anglos in Colorado. In the New York City BRFSS, Hispanics had higher levels of physical inactivity, defined as exercise fewer than 3 times per week, than whites (17). There were no significant ethnic differences in physical inactivity, which incorporated work and leisure-time, in the Stanford Five-City Project (15). An analysis of NHANES III that focused on women, reported that Hispanic women were more likely to do no leisure-time physical activity than white women (4). In a comparison of no leisure-time physical activity using national BRFSS data for 2000, Hispanics were more likely to be sedentary than whites for all persons except those age 65-74 years (6). Like other studies we were unable to incorporate work-related activity into our measure of physical inactivity, which tends to underestimate total amount of physical activity because Hispanics' employment is more likely to be physically active than whites' employment.

The higher consumption of fruits or vegetables among Hispanics compared to whites in our study differs from most, but not all, studies of ethnic differences of fruit or vegetable consumption. A comparison of the Hispanic Health and Nutrition Examination Survey (HHANES) with NHANES II showed that Mexican American women consumed fewer servings of fruits or vegetables than white women (20). Shea et al. (21) completed telephone interviews modeled after the BRFSS in New York City and reported lower consumption of vegetables among Latinos than among whites. Otero-Sabogal et al. (22) conducted telephone interviews in the San Francisco Bay Area Study and found that Latinos were more likely to eat fewer than three servings of fruits or vegetables on the previous day than whites. Using personal interview data from the Stanford Five-City Project, Winkleby et al. (23) reported no difference in fruit or vegetable consumption by ethnicity. Winkleby and Cubbin (6) used national BRFSS data in 2000 to assess low fruit or vegetable intake, defined as less than 3 servings per day, and found

with the exception of the 45-64 year age group Hispanics had lower levels of low fruit or vegetable intake than whites (6). Our findings, like those of Winkleby and Cubbin (6), may reflect the greater importance of socioeconomic status than ethnicity for fruit or vegetable intake since adjustment for socioeconomic status reversed the unadjusted positive associations.

The ethnic differences we saw for drinking differed by residence and gender. Hispanic females who lived on the border were more likely to drink heavily than white females, while Hispanic females who did not live on the border were less likely to drink heavily than white females. Binge drinking was lower among Hispanic women than white women regardless of residence. There was little difference in ethnicity for heavy drinking among men. Hispanic men who lived on the border were less likely to binge drink than white men, but Hispanic men who did not live on the border were more likely to binge drink. Results of other studies of ethnic differences in drinking have been mixed. Otero-Sabogal et al. (22) reported lower rates of any drinking in the past month and higher rates of binge drinking among Latinos overall than among whites in the San Francisco Bay Area Study. The San Francisco BRFSS found lower rates of any drinking in Latinos than whites of both genders, but no difference in binge drinking (18). In a nationally representative survey that used personal interviews, Caetano and Clark (24) reported higher rates of binge drinking among Hispanic men than among white men. There were no significant differences in drinking between Mexican Americans and whites in the Stanford Five-City Project (15). Guendelman and Abrams (20) reported much lower levels of drinking among Mexican American women in HHANES than among white women in NHANES II. In a study conducted on the US-Mexico border that utilized personal interviews, Holck et al. (25) reported that Mexican American women were more likely to abstain from alcohol than Anglo women. The differing effect of residence on heavy drinking in females and on binge drinking in males in

our study may be a function of socioeconomic status since adjustment for socioeconomic status reversed the negative association among females and the positive association among males.

We found a lower likelihood of current smoking among Hispanics compared with whites regardless of border residence. This finding is in agreement with the majority of studies of this topic (4, 6, 15, 17, 18, 20, 23). One exception is the San Francisco Bay Area Study which reported no ethnic differences for current smoking, but did find that Latinos were more likely to be never smokers than whites (22). Another exception is the San Luis Valley Diabetes Study which reported a non-significantly higher prevalence of current smoking among Hispanic females than among Anglo females (19). In our study, Hispanic men were more likely to smoke than white men prior to adjustment for socioeconomic status indicating that smoking among males may be related more to socioeconomic status than to ethnicity.

This study was not without limitations. Incomplete telephone coverage (2000 Texas whites 98%; Hispanics 94%) (26), and low response rates may have introduced selection bias. Especially if persons less likely to engage in risk behaviors were more likely to respond to the survey. We were unable to determine whether response rates differed by ethnicity or border residence which, had they differed, would have resulted in substantial bias. Risk behaviors are based on self-report and are prone to misclassification. An additional limitation of our study is the failure of the BRFSS to breakdown Hispanic ethnicity into its component parts. Although the majority of Hispanics in the Texas BRFSS are Mexican American, other Hispanic groups with differing risk profiles are included. Small numbers of border residents limited study power to assess effect modification. Analysis at the county level may be a limitation since socioeconomic status of census tracts within counties tends to vary substantially. Future research

of this issue should examine census tracts or distance from the border as a community-level measure of socioeconomic status.

To our knowledge, this is the first study to assess ethnic differences in health behaviors using proximity to the US-Mexico border as a community-level measure of socioeconomic status. We hypothesized that ethnic differences would be more striking among border residents than among non-border residents due to the extreme poverty of the Texas-Mexico border region. This was not the case and most associations were weaker for border residents than for non-border residents. The one behavior that exhibited effect modification, binge drinking among males, showed a negative association among border residents and a positive association among non-border residents. Possible explanations for these findings are: 1) whites on the border are of lower socioeconomic status than non-border whites which may influence risk behaviors, or 2) whites on the border engage in risky health behaviors more often than non-border whites. The average median household income for 1999 among whites for the 15 border counties ($36,563) was similar to that among whites for the remaining 239 counties ($37,246), which was not the case for Hispanics (border $21442, non-border $26640) (26). Acculturation may be defined as a non-dominant group adopting the cultural attitudes, values and behaviors of a dominant group. The dominant group on the Texas-Mexico border is Hispanic accounting for 85% of residents of the 15 Texas counties bordering Mexico in 2000 (12). Thus, whites living on the border may have adopted the risk behaviors of the dominant Mexican culture. Future studies of ethnic differences should assess adoption of the Mexican culture by whites living in predominantly Hispanic areas. Results of this study would argue against targeting specific ethnic groups for behavioral risk factor interventions in favor of universal interventions that can be adapted to be culturally appropriate for all people.

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Table 1. Distribution of potential confounding factors among non-border and border whites and Hispanics by gender

	WOMEN			
	Non-border		Border	
	White	Hispanic	White	Hispanic
	(n=10,046)	(n=2,979)	(n=306)	(n=1,131)
Variable	Weighted %	Weighted %	Weighted %	Weighted %
Age group (years)				
18-24	9.9	20.4	5.2	15.1
25-44	35.6	51.0	29.3	44.7
45-64	32.2	22.0	29.8	29.7
≥65	22.3	6.6	35.7	10.5
Educational level				
< High school	9.0	45.2	9.0	44.2
High school graduate	28.2	25.8	22.8	25.1
Some college	30.7	18.1	33.2	18.8
College graduate	32.1	10.9	35.0	11.9
Annual household income				
<$15,000	10.5	24.4	13.1	33.9
$15,000-$24,999	16.0	33.0	15.1	30.7
$25,000-$44,999	33.7	27.5	37.4	26.2
$45,000-$74,999	17.5	8.6	20.1	5.7
≥$75,000	22.3	6.5	14.3	3.5
Poor or fair perceived general health	15.8	32.1	19.4	34.6
Diabetes	5.9	8.0	8.3	8.1
	MEN			
	Non-border		Border	
	White	Hispanic	White	Hispanic

	(n=6,858)	(n=1,954)	(n=215)	(n=591)
Variable	Weighted %	Weighted %	Weighted %	Weighted %
Age group (years)				
18-24	11.4	22.7	10.6	20.0
25-44	38.2	54.0	28.1	46.0
45-64	33.8	20.1	30.0	24.7
≥65	16.6	3.2	31.3	9.3
Educational level				
<High school	7.7	44.5	4.9	34.0
High school graduate	25.2	28.0	23.9	32.2
Some college	27.2	17.2	31.6	21.5
College graduate	39.9	10.3	39.6	12.3
Annual household income				
<$15,000	5.6	20.4	6.8	30.3
$15,000-$24,999	12.8	33.3	16.6	30.5
$25,000-$44,999	33.0	31.5	37.0	26.8
$45,000-$74,999	20.3	8.0	16.1	7.8
≥$75,000	28.3	6.8	23.5	4.6
Poor or fair perceived general health	13.6	27.8	11.5	25.1
Diabetes	6.8	6.4	9.7	7.0

Table 2. Prevalence of risk behaviors among non-border and border whites and Hispanics by gender

	WOMEN			
	Non-border		Border	
	White	Hispanic	White	Hispanic
Behavior	Weighted %	Weighted %	Weighted %	Weighted %
Overweight	46.3	63.1	50.3	65.4
Obese	19.1	29.9	21.8	31.5
Physically inactive	24.9	42.0	24.4	38.6
Consumed < 5 fruits or vegetables per day	71.8	74.1	67.6	73.8
Heavy drinking	5.5	3.0	2.8	2.3
Binge drinking	8.6	9.0	5.9	5.9
Smoking	22.4	12.6	19.8	11.5
	MEN			
	Non-border		Border	
	White	Hispanic	White	Hispanic
Behavior	Weighted %	Weighted %	Weighted %	Weighted %
Overweight	68.4	70.2	72.2	72.7
Obese	23.0	27.4	18.3	27.8
Physically inactive	20.5	38.3	15.0	25.6
Consumed < 5 fruits or vegetables per day	81.3	82.8	80.4	84.9
Heavy drinking	7.5	9.3	6.2	7.7
Binge drinking	24.0	35.3	25.4	30.7
Smoking	25.1	29.2	19.8	25.6

Table 3. Odds ratios for risk behaviors among non-border and border Hispanics relative to whites by gender

	WOMEN			
	Non-border		Border	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Behavior	OR (95% CI)	OR* (95% CI)	OR (95% CI)	OR* (95% CI)
Overweight	1.98 (1.73-2.27)	1.79 (1.48-2.17)	1.86 (1.32-2.62)	1.36 (0.89-2.09)
Obese	1.81 (1.57-2.08)	1.48 (1.29-1.70)	1.65 (1.24-2.20)	1.15 (0.72-1.86)
Physically inactive	2.19 (1.77-2.71)	1.35 (1.14-1.58)	1.95 (1.73-2.19)	1.44 (0.89-2.33)
Consumed < 5 fruits or vegetables per day	1.12 (0.87-1.45)	0.77 (0.63-0.94)	1.35 (0.72-2.54)	0.82 (0.39-1.72)
Heavy drinking	0.54 (0.41-0.70)	0.60 (0.39-0.94)	0.81 (0.19-3.48)	1.41 (0.23-8.68)
Binge drinking	1.05 (0.82-1.35)	0.83 (0.70-0.99)	1.01 (0.47-2.18)	0.62 (0.25-1.57)
Smoking	0.50 (0.39-0.64)	0.26 (0.18-0.38)	0.53 (0.30-0.93)	0.30 (0.15-0.62)
	MEN			
	Non-border		Border	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Behavior	OR (95% CI)	OR* (95% CI)	OR (95% CI)	OR* (95% CI)
Overweight	1.09 (0.82-1.45)	1.36 (1.02-1.81)	1.03 (0.68-1.55)	1.20 (0.70-2.08)
Obese	1.26 (0.98-1.63)	1.26 (0.94-1.68)	1.72 (1.05-2.81)	1.43 (0.84-2.45)
Physically inactive	2.41 (2.13-2.71)	1.33 (1.10-1.60)	1.95 (1.43-2.66)	0.97 (0.47-2.02)
Consumed < 5 fruits or vegetables per day	1.10 (0.90-1.36)	0.81 (0.68-0.97)	1.36 (0.77-2.42)	0.83 (0.46-1.51)
Heavy drinking	1.27 (0.94-1.73)	0.97 (0.66-1.44)	1.27 (0.67-2.42)	1.06 (0.70-1.62)
Binge drinking	1.73 (1.39-2.14)	1.21 (0.99-1.49)	1.30 (0.86-1.97)	0.90 (0.49-1.63)
Smoking	1.23 (1.05-1.45)	0.57 (0.49-0.67)	1.39 (0.59-3.25)	0.78 (0.28-2.18)

OR = odds ratio; CI = confidence interval.
*Adjusted for age, educational level, annual household income, perceived general health and diabetes.

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A Multilevel Analysis of Socioeconomic Status and Prostate Cancer Risk

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Abstract

Purpose: We investigated whether prostate cancer was associated with socioeconomic status (SES) at the individual-level, the area-level or a combination of both levels.

Methods: This population-based case-control study of prostate cancer among men aged 65-79 years was conducted between 2000 and 2002 in South Carolina. Complete interviews were available for 407 incident prostate cancer cases and 393 controls (with respective response rates of 61% and 64%). We used educational level to measure individual-level SES, and a composite variable capturing income and education from 2000 Census data to measure area-level SES.

Results: After adjustment for race, age, geographical region, and PSA testing, men with some college were at reduced risk of prostate cancer (odds ratio [OR] 0.44, 95% confidence interval [CI] 0.27-0.72) as were men in the highest quartile of area-level SES (OR 0.52, 95% CI 0.34-0.80). When assessing individual-level and area-level SES simultaneously and accounting for their non-independence, the independent negative associations persisted and appeared to be more striking among men diagnosed with localized disease rather than advanced disease.

Conclusions: The independent effects of area-level and individual-level SES on prostate cancer risk seen in our study may help explain the conflicting results of previous studies conducted at both levels.

Keywords: prostate cancer, socioeconomic status, multilevel analysis, case-control studies

List of Abbreviations and Acronyms

CI – Confidence interval

OR – Odds ratio

PSA – Prostate specific antigen

SES – Socioeconomic status

US – United States

Introduction

Prostate cancer is the most frequently diagnosed cancer in the United States (US), and the second leading cause of cancer deaths among men. Little is understood about the etiology of prostate cancer nor do we know what factors might explain why African-American men are at greater risk relative to white men. Several studies have investigated prostate cancer incidence associated with individual-level socioeconomic status (SES) based on income, occupation or educational level with conflicting results. We limit our review to studies conducted in the US, because SES level differs across countries. Two of the four studies that evaluated the association between individual-level SES and prostate cancer incidence in the US reported positive associations (1,2), while two reported no association (3,4). Of the seven studies that investigated area-level SES and prostate cancer incidence in the US, three studies each reported a positive association (5-7) or no association (8-10), while one study reported a negative association (11). Proposed mechanisms for explaining the positive association between individual-level and area-level SES and prostate cancer are consuming a healthy diet (4), engaging in exercise (4), and increased access to screening (12).

Studies of SES and prostate cancer must account for screening since the effect of high SES on prostate cancer risk may have differed before and after the advent of prostate specific antigen (PSA) testing. Before PSA testing higher SES men were more likely to have lower rates of prostate cancer as a result of engaging in healthy behaviors (4). After PSA testing higher SES men were more likely to be screened annually (12), and thus more likely to be diagnosed with the disease, especially at an earlier stage (13). Using 1987 as the year that PSA testing became widespread, the majority of individual-level (1,2,4) and half of the area-level (8-11) studies of

SES and prostate cancer were conducted before screening which may help explain the mixed results.

Along with the failure to account for PSA testing, another possible explanation for the mixed results of the SES and prostate cancer association is the failure to account for area-level SES in studies of individual-level SES and vice versa. Several studies have investigated the joint effects of individual-level and area-level SES and cardiovascular disease incidence (14,15) and mortality (16-17); however, few have focused on cancer (17,18, 19). Robert et al. (18) recently investigated the joint effect of individual-level and area-level SES on breast cancer incidence and found that area-level SES was positively associated with breast cancer after adjustment for individual-level SES, while the reverse was not true. In contrast, Steenland et al. (19) found little effect of area-level SES on prostate cancer mortality after adjustment for individual-level SES. Borrell et al. (17) found higher rates of cancer mortality among blacks and whites in the Atherosclerosis Risk in Communities Study who resided in neighborhoods with the lowest SES score that was weakened by adjustment for individual-level SES. To our knowledge no other studies have simultaneously investigated the effect of individual-level and area-level measures of SES on prostate cancer risk. We assessed the joint effects of area-level SES and individual-level SES to indirectly determine whether conflicting results for prostate cancer incidence associated with individual-level SES may have been due to the unmeasured influence of area-level SES.

Materials and Methods

Detailed methods of this population-based case-control study conducted in South Carolina from 2000-2002 appear elsewhere (20). Briefly, cases diagnosed with primary invasive prostate cancer between October 1999 and September 2001 were identified through the South Carolina Central Cancer Registry. During this time, the South Carolina Central Cancer Registry was certified as silver by the North American Association of Central Cancer Registries with a case ascertainment rate between 90% and 95% (21). Eligible cases were South Carolina residents who were Caucasian or African-American, aged 65-79, whose prostate cancer was histologically confirmed, and whose physicians had given permission for research staff to contact their patient. We selected all eligible cases with advanced disease (stages III and IV), and a random sample of men with localized disease (stages I and II). We had insufficient funding to study all men with localized disease. Because we wanted approximately equal numbers of men with localized disease by race, we performed stratified sampling by race and oversampled African-American men by randomly selecting 82% of men with localized disease compared with 40% of Caucasian men with localized disease. Of the 692 eligible prostate cancer cases, 425 (61.4%) completed a standardized telephone interview. Of the remaining eligible cases, 90 physician refused (13.0%), 71 patient refused (10.3%), 24 died prior to the interview (3.5%), 59 were not located (8.5%), and 23 were too sick to participate (3.3%).

Control subjects were randomly sampled from the 1999 Health Care Financing Administration Medicare beneficiary file. Controls were frequency matched to cases on age (5-year age groups), race (Caucasian, African-American), and geographical region (western 14 counties, middle 19 counties and eastern 13 counties of the state). Eligible controls were South

Carolina residents, aged 65-79, with no history of prostate cancer. Of the 756 eligible controls, 482 (63.8%) completed the interview. Of the remaining eligible controls, 108 refused (14.3%), 22 died prior to the interview (2.9%), 112 were not located (14.8%), and 32 were too sick to participate (4.2%). We eliminated 59 subjects (7 cases and 52 controls) who upon review of medical records were determined to have prevalent prostate cancer. After excluding an additional 48 subjects (11 cases and 37 controls) who completed fewer than ten questions, the final sample size was 800 subjects (407 cases and 393 controls).

Institutional Review Boards of the University of South Carolina, the Centers for Disease Control and Prevention, and the National Cancer Institute approved this project's data collection procedures. Interviewing began in June 2000 and was completed in August 2002. Trained interviewers from the University of South Carolina Survey Research Laboratory conducted computer-assisted telephone interviews with subjects who provided verbal consent with the understanding that written consent would be obtained. The questionnaire collected information on demographic characteristics, socioeconomic status, stress, coping, alcohol and tobacco use, physical activity, diet, medical history, family history of cancer, history of sexually transmitted diseases, and farm-related work activities and exposures. Most exposures pertained to the period prior to a reference date, the date of diagnosis for cases and an assigned date for controls that was comparable to the distribution of diagnosis dates among cases.

We used the Generalized Linear Latent and Mixed Models macro in STATA 8 to estimate the odds ratio of prostate cancer associated with individual-level and area-level SES while accounting for their non-independence and controlling for potential confounding factors (22). We had a two level hierarchical structure; therefore, we fit a two-random level intercepts logistic model and used RESET diagnostic test to evaluate misspecification of error or

inappropriate link function (23). Since the majority of men were retired we used educational level to measure individual-level SES rather than annual household income one year prior to diagnosis. There were five categories of educational level: 1) less than 8^{th} grade, 2) 9^{th} to 11^{th} grade, 3) high school graduate, 4) some college or technical school, and 5) college graduate or more. To measure area-level SES we created a composite variable consisting of median household income, percent of persons living below the poverty level, percent unemployment, and percent college or higher educational attainment addressing four of the six domains thought to comprise socioeconomic position in the US (24). Subjects' addresses were not geocoded, therefore this information was available at the zip code level from the 2000 census (25). Of the total of 919 zip codes in South Carolina, 265 were represented in the study. To ensure sufficient sample sizes and to minimize overdispersion of the estimates, we collapsed zip codes of homogeneous geographic and demographic characteristics into groups with a minimum of 25 subjects in each. There were 21 groupings ranging from 29 to 57 subjects (median=41). We reversed the coding of poverty level and unemployment, summed the four area-level measures of SES, and categorized the composite variable using the quartile distribution among controls. The Cronbachs' alpha for this composite variable was 0.83 among controls indicating these items went together in measuring the area-level SES construct.

Individual-level variables assessed as confounders included marital status, family history of prostate cancer, body mass index, and frequency of PSA testing as categorized in Table 1. Body mass index, defined as self-reported weight in kilograms before reference date divided by the square of self-reported height in meters, was categorized using the quartile distribution among controls. PSA testing was categorized as frequency within the past 5 years with men who reported they had a PSA test but did not remember the number of tests categorized as 1-2 tests

(53 local cases, 10 advanced cases, 90 controls). Controls were frequency matched to cases on age, race, and geographical region thus we adjusted for these three factors based on the study design. We also adjusted for PSA testing since it was the only variable to materially change the unadjusted odds ratios. Although PSA testing may be in the causal pathway between SES and prostate cancer we adjusted for it to investigate the association between SES and prostate cancer accounting for the effect of SES on PSA testing. In analyses by stage at diagnosis, men with stages I and II were classified as having localized disease, and men with stages III and IV were classified as having advanced disease. Stages I and II corresponded to tumors that were clinically inapparent or confined within the prostate with no nodal involvement or metastases (26). Stages III and IV corresponded to tumors that extended through the prostatic capsule or invaded adjacent structures with or without nodal involvement or metastases. Linear trend was assessed by treating categorical variables as continuous variables.

Results

Table 1 compares cases by stage at diagnosis and controls for demographic and socioeconomic factors. Compared to controls prostate cancer cases were more likely to be younger, to reside in the middle portion of the state, to be married or living as married, to have a family history of prostate cancer, to have undergone PSA testing, to have a lower educational level themselves, and to live in a community with a lower composite socioeconomic status. A higher percentage of men diagnosed with localized disease were African-American and in the lowest quartile of body mass index than men diagnosed with advanced disease, while the reverse was true of men diagnosed with advanced disease.

The odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer associated with individual-level and area-level SES are shown in Table 2. There were significant correlations between PSA testing and individual-level (Spearman $r=0.30$, $p<0.0001$) and area-level (Spearman $r=0.09$, $p=0.007$) SES (data not shown). After adjustment for race, age, geographical region, and PSA testing, men with some college or technical school were at significantly reduced risk (OR 0.44, 95% CI 0.27-0.72) and college graduates were at borderline reduced risk (OR 0.67, 95% CI 0.42-1.05) of prostate cancer. Combining these upper two categories resulted in a significantly reduced risk of prostate cancer (OR 0.55, 95% CI 0.35-0.87). Similarly, men in the highest quartile of area-level SES (OR 0.52, 95% CI 0.34-0.80) were at reduced prostate cancer risk. In both measures of SES there was a trend of decreasing risk with increasing educational level. Although the trend test was significant for individual-level SES, it must be noted that the referent group was markedly higher than all other educational groups and that the trend test is driven by this group. Additional adjustment for

individual-level SES or area-level SES and accounting for the non-independence of these measures, resulted in independent negative associations for prostate cancer among men with some college (OR 0.45, 95% CI 0.27-0.78) and among men in the highest quartile of area-level SES (OR 0.52, 95% CI 0.25-1.10).

Risk of prostate cancer associated with socioeconomic factors by stage at diagnosis is presented in Table 3. With one exception, the third quartile of area-level SES among men diagnosed with advanced disease, there were reductions in risk associated with individual-level SES and area-level SES regardless of stage at diagnosis. The decreased risk among men with some college or technical school and among men who lived in the highest quartile of area-level SES was weaker among men diagnosed with advanced cancer than among men diagnosed with localized cancer but remained reduced even after adjustment for the other level measure of SES.

Discussion

We found a significantly reduced risk of prostate cancer associated with having some college or technical school and a borderline reduced risk for the highest category of our individual-level SES measure, educational level. In addition there was a significant trend of decreasing risk with increasing educational level. A possible explanation for the trend is the higher percentage of cases (especially those with localized disease) that had an elementary education than controls. Although not limited to men diagnosed with localized disease, the reduction in risk in the two highest SES categories was more pronounced among this group. Our results are in conflict with the majority of the studies of individual-level SES and prostate cancer risk which reported a positive association (1,2) or no association (3,4). Possible explanations for our findings relate to the educational level and race of men in our study. Men in our study were fairly low SES; 36.8% of our controls age 65 and over had less than a high school education in comparison with 31.2% of men in the US in 1999 (27). The only study of individual-level SES and prostate cancer conducted since the advent of PSA testing found no association after adjustment for PSA testing among the highly educated, younger American Cancer Society Nutrition Cohort Study; 8% of their participants age 55 and over had less than a high school education (3) compared to 26% of men in the US in 1999 (27). A large percentage of men in our study were African-American (40.8% of cases; 42.2% of our controls). Yu et al. (2) reported a weak positive association between college education and prostate cancer risk among Caucasian men, but not among African-American men.

Similarly, prostate cancer was negatively associated with area-level SES measured by our composite variable. Again, the reduction in risk was stronger among men diagnosed with

localized disease than among men diagnosed with advanced disease. The negative association we found was in contrast to most previous studies of area-level SES and prostate cancer that reported a positive association (5-7) or no association (8-10). In their study of area-level SES and prostate cancer mortality using the American Cancer Society Nutrition Cohort Study, Steenland et al. (Dr. Kyle Steenland, personal communication, February 9, 2006) found a positive association. Possible explanations for our findings relate to the race of men in our study, and the different measures of area-level SES used by different studies. As indicated previously, over 40% of our participants were African-American. One study identified a positive association in all racial groups except whites (6), another study found a positive association in all racial groups except Asians (8), and another study reported no association in African-American or Caucasian men (9). Studies of area-level SES have used a variety of measures including a combination of occupation and poverty level (5), median household income (6), a combination of median household income and educational attainment (7), and a combination of household income, home value, occupation and education (19).

After performing a multilevel analysis, there was little effect on either measure of SES with approximately the same reduction in prostate cancer risk associated with the two highest levels of individual-level SES combined (OR 0.55, 95% CI 0.35-0.87) as the highest quartile of area-level SES (OR 0.52, 95% CI 0.25-1.10). These results were evident for men diagnosed with localized and advanced disease; however, the association was more pronounced among men with localized disease. This is in contrast to the majority of studies of SES and cardiovascular disease incidence and mortality which reported stronger associations for individual-level SES than for area-level SES after simultaneous adjustment (14-17). In the American Cancer Society Nutrition Cohort Study, Steenland et al. (Dr. Kyle Steenland, personal communication, February 9, 2006)

found no association between individual-level SES and prostate cancer mortality after adjustment for area-level SES and vice versa. However, the only study of cancer incidence to examine the joint effects of individual-level and area-level SES reported a stronger effect of area-level SES than individual-level SES (18). These investigators hypothesized the stronger positive effect of area-level than individual-level SES they saw on breast cancer risk may have been due to greater access to mammograms in higher SES areas (28), or to physical and environmental characteristics common in the community that may increase a woman's breast cancer risk. One possible explanation for the reduced prostate cancer risk associated with higher individual-level and area-level SES we saw is that higher SES men and those living in higher SES areas are less likely to undergo PSA testing. This was not the case in our study where PSA testing was positively and significantly correlated with both measures of SES (individual-level SES Spearman r=0.30, p-value<0.0001; area-level SES Spearman r=0.09, p-value=0.007). An alternative explanation for the reduced risk of prostate cancer associated with high individual-level and area-level SES is that higher SES men and those from higher SES areas have greater access to healthful diets and physical activity.

This study was not without limitations. Our response rates were lower than desired and we sampled men with localized disease somewhat limiting the generalizability of our results and possibly resulting in some non-significant reductions in prostate cancer risk. African-American men with advanced disease were less likely to participate than African-American men with localized disease which limited study power to statistically assess effect modification by race and stage. We were unable to determine whether non-participation rates of cases and controls differed by socioeconomic status. However, comparable percentages of non-respondents (22.6%) and respondents (25.2%) were diagnosed with advanced disease which would argue

against selective survival of cases. The average length of time between diagnosis and interview was 8.7 months, which may have led to misclassification. Another source of misclassification was the memory problems common in men age 65 years and over. Our study power was limited for some joint effects due to small numbers. We were unable to assess race as an effect modifier of the association between SES and prostate cancer due to small numbers. Analysis at the grouped zip code level in our study may not reflect the area-level SES accurately since socioeconomic status of block groups and census tracts within zip codes tend to vary substantially (24). Although block groups and census tracts may better represent area-level SES than grouped zip codes, we chose to group zip codes to provide stable estimates.

Our study is the first population-based case-control study of prostate cancer to simultaneously assess the effect of individual-level and area-level SES on prostate cancer risk. Additional strengths of the study included the fairly large number of men with advanced disease which allowed us to perform analyses by stage at diagnosis, and utilizing an accepted measure of area-level SES (24). We adjusted for the frequency of PSA testing in an attempt to isolate the effect of SES apart from its influence on access to care. Area-level SES may be a more comprehensive measure of SES than individual-level SES because it captures social characteristics of communities that are not typically measured (29). The independent effects of area-level and individual-level SES on prostate cancer risk seen in our study may help explain the conflicting results of previous studies conducted at both levels and would argue for the measurement of both levels in future studies.

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Table 1. Comparison of cases by stage at diagnosis and controls for demographic and socioeconomic factors

	Localized Cases (n=314)	Advanced Cases (n=102)	Controls (n=429)
	N (%)	N (%)	N (%)
Race			
Caucasian	175 (55.7)	70 (68.6)	258 (60.1)
African-American	139 (44.3)	32 (31.4)	171 (39.9)
Age (years)			
65-69	138 (44.0)	54 (52.9)	186 (43.4)
70-74	102 (32.5)	32 (31.4)	125 (29.1)
75-79	74 (23.5)	16 (15.7)	118 (27.5)
Geographical region			
Eastern counties	180 (57.3)	55 (53.9)	243 (56.6)
Middle counties	81 (25.8)	26 (25.5)	92 (21.5)
Western counties	53 (16.9)	21 (20.6)	94 (21.9)
Marital status[a]			
Single/Separated/Divorced/ Widowed	56 (18.6)	17 (17.0)	80 (20.6)
Married/Living as married	245 (81.4)	83 (83.0)	308 (79.4)
Missing	5	1	5
Family history[a]			
None	212 (70.9)	66 (66.7)	329 (84.6)
First-degree	63 (21.1)	23 (23.2)	43 (11.0)

Second-degree	24 (8.0)	10 (10.1)	17 (4.4)
Missing	7	2	4
Body mass index (quartiles) [a]			
<24.4	77 (25.9)	13 (13.1)	90 (23.5)
24.4-27.2	83 (28.0)	31 (31.3)	101 (26.3)
27.3-29.8	69 (23.2)	27 (27.3)	96 (25.1)
≥29.9	68 (22.9)	28 (28.3)	96 (25.1)
Missing	9	2	10
Number of PSA tests in past 5 years			
0	43 (13.7)	18 (17.7)	98 (22.9)
1-2	102 (32.5)	29 (28.4)	154 (36.0)
3-4	48 (15.3)	19 (18.6)	66 (15.4)
≥5	121 (38.5)	36 (35.3)	110 (25.7)
Missing	1	0	0
Educational level			
Elementary education	84 (26.8)	22 (22.2)	89 (20.7)
Some high school	44 (14.1)	11 (11.1)	69 (16.1)
High school graduate	78 (24.9)	23 (23.2)	102 (23.8)
Some college or technical school	37 (11.8)	17 (17.2)	77 (18.0)
College graduate	70 (22.4)	26 (26.3)	92 (21.5)
Missing	1	3	0
Composite socioeconomic status (quartiles)			
Low SES	105 (33.4)	30 (29.4)	118 (27.5)

Medium SES	94 (29.9)	18 (17.7)	115 (26.8)
High SES	71 (22.6)	35 (34.3)	106 (24.7)
Very high SES	44 (14.0)	19 (18.6)	90 (21.0)

[a] Consists of 306 local cases, 101 advanced cases and 393 controls.

Table 2. Odds ratios for prostate cancer associated with individual-level and area-level socioeconomic factors

	OR[a] (95% CI)	OR[b] (95% CI)	OR[c] (95% CI)
Educational level			
Elementary education	1.00 (Referent)	1.00 (Referent)	
Some high school	0.60 (0.37-0.95)	0.57 (0.34-0.94)	
High school graduate	0.69 (0.45-1.06)	0.70 (0.44-1.11)	
Some college or technical school	0.44 (0.27-0.72)	0.45 (0.27-0.78)	
College graduate	0.67 (0.42-1.05)	0.65 (0.39-1.07)	
P for trend	0.05	0.08	
Composite socioeconomic status (quartiles)			
Low SES	1.00 (Referent)		1.00 (Referent)
Medium SES	0.79 (0.53-1.17)		0.78 (0.38-1.59)
High SES	0.86 (0.58-1.28)		0.96 (0.42-2.23)
Very high SES	0.52 (0.34-0.80)		0.52 (0.25-1.10)
P for trend	<0.01		0.13

[a] Adjusted for race, age, geographical region, and PSA testing.

[b] Adjusted for race, age, geographical region, composite socioeconomic status, and PSA testing.

[c] Adjusted for race, age, geographical region, educational level, and PSA testing.

Table 3. Odds ratios for prostate cancer associated with individual-level and area-level socioeconomic factors by stage at diagnosis

	OR[a] (95% CI)	OR[b] (95% CI)	OR[c] (95% CI)
		Localized	
Educational level			
Elementary education	1.00 (Referent)	1.00 (Referent)	
Some high school	0.60 (0.36-0.98)	0.54 (0.31-0.93)	
High school graduate	0.70 (0.44-1.11)	0.70 (0.43-1.16)	
Some college or technical school	0.39 (0.22-0.67)	0.41 (0.23-0.73)	
College graduate	0.62 (0.38-1.02)	0.61 (0.35-1.05)	
P for trend	0.03	0.06	
Composite socioeconomic status (quartiles)			
Low SES	1.00 (Referent)		1.00 (Referent)
Medium SES	0.87 (0.58-1.32)		0.88 (0.40-1.96)
High SES	0.72 (0.47-1.11)		0.80 (0.35-1.83)
Very high SES	0.48 (0.30-0.76)		0.51 (0.21-1.21)
P for trend	<0.01		0.10
		Advanced	
Educational level			
Elementary education	1.00 (Referent)	1.00 (Referent)	
Some high school	0.54 (0.24-1.21)	0.61 (0.26-1.42)	
High school graduate	0.67 (0.33-1.34)	0.69 (0.32-1.45)	
Some college or technical school	0.58 (0.27-1.25)	0.54 (0.24-1.26)	
College graduate	0.77 (0.37-1.59)	0.74 (0.34-1.64)	

P for trend	0.62	0.49	
Composite socioeconomic			
status (quartiles)			
Low SES	1.00 (Referent)		1.00 (Referent)
Medium SES	0.56 (0.28-1.10)		0.57 (0.24-1.36)
High SES	1.32 (0.72-2.40)		1.41 (0.63-3.17)
Very high SES	0.72 (0.37-1.39)		0.66 (0.26-1.65)
P for trend	0.84		0.74

[a] Adjusted for race, age, geographical region, and PSA testing.

[b] Adjusted for race, age, geographical region, composite socioeconomic status, and PSA testing.

[fc] Adjusted for race, age, geographical region, educational level, and PSA testing.

Meeting Abstract: Sanderson M, Daling JR, Malone KE, Doody DR, Porter PL. Perinatal factors and mortality from breast cancer. 4th Department of Defense Breast Cancer Research Program Meeting, Philadelphia, PA, June 2005.

PERINATAL FACTORS AND MORTALITY FROM BREAST CANCER

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Associations have been reported between characteristics of the intrauterine environment and subsequent risk of chronic diseases including breast cancer. In the current study, we assessed whether perinatal factors were associated with mortality from breast cancer.

This follow-up study consists of breast cancer cases who participated in two population-based case-control studies of breast cancer in women age 44 or younger conducted between 1983 and 1992 in three western Washington counties. This analysis is restricted to the 1024 cases or their proxies who completed a supplementary questionnaire on perinatal factors from 1994 to 1996. The mean length of follow-up was 110.4 months.

Perinatal factors that appeared to be associated with reduced mortality from breast cancer included being born second or higher in the birth order (hazard ratio [HR] = 0.2, 95% confidence interval [CI] 0.1-0.3) and maternal smoking (HR = 0.7, 95% CI 0.5-1.0). Factors for which we observed some evidence of a possible increase in breast cancer mortality were birthweight of 4000 grams or more (HR = 3.4, 95% CI 0.9-13.9) and being more than 4 weeks postterm (HR = 3.3, 95% CI 0.5-24.0).

The most popular mechanism proposed to explain associations between perinatal factors and breast cancer risk relates to in utero estrogen exposure by which certain conditions increase or decrease pregnancy estrogen levels. It is unclear whether this mechanism may play a role in breast cancer mortality, however our findings on birth order, maternal smoking and birthweight appear to support the hypothesis, while our gestational age result conflicts with the hypothesis. The protective effect of being born second or higher in the birth order is striking and needs to be confirmed in future studies.

Original work supported by the U.S. Army Medical Research and Materiel Command under DAMD17-00-1-0340 and current work supported by DAMD17-03-1-0274.

Meeting Abstract: Peltz G, Sanderson M, Perez A, Estrada JK, Johnson M. Use of mammography by Texas-Mexico border residence and ethnicity. 4th Department of Defense Breast Cancer Research Program Meeting, Philadelphia, PA, June 2005.

USE OF MAMMOGRAPHY BY TEXAS-MEXICO BORDER RESIDENCE AND ETHNICITY

Gerson Peltz, M.D., Maureen Sanderson, Ph.D., Adriana Perez, Ph.D., Joselito K. Estrada, Ph.D., Matthew Johnson, Ph.D.
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Mexican American women age 40 and over, especially those who are less acculturated to the US culture, tend to have fewer, less frequent mammograms than non-Hispanic white women. Acculturation, defined as a non-dominant group adopting the cultural attitudes, values and behaviors of a dominant group, typically pertains to adoption of the US culture. The dominant group on the Texas-Mexico border is Mexican American; therefore, we may see non-Hispanic white women residing on the border adopting the dominant Mexican culture by having fewer, less frequent mammograms. We examined whether use of mammography among non-Hispanic white women residing on the Texas-Mexico border was more comparable to non-border non-Hispanic white women or to border Mexican American women.

Using data from the Texas statewide Behavioral Risk Factor Surveillance System (BRFSS) for the years 1999, 2000 and 2002, we compared women who resided in one of the 15 counties contiguous with the Mexico border to non-border residents. This analysis is restricted to women age 40 and over whose self-identified racial/ethnic group was non-Hispanic white or Hispanic which resulted in 456 border residents and 4,431 non-border residents.

After adjustment for age, educational level, and insurance coverage, border non-Hispanic white women were more likely (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.1-3.7) than non-border non-Hispanic white women to have ever had a mammogram, but border and non-border Mexican American women were not. Relative to non-border non-Hispanic white women, Mexican American women (border OR 1.1, 95% CI 1.0-1.3; non-border OR 1.3, 95% CI 1.0-1.7) and border non-Hispanic white women (OR 1.3, 95% CI 0.8-2.1) were slightly more likely to have had a mammogram in the past two years.

For the most part, use of mammography appeared to be more similar among members of the same ethnic group than among residents of the same geographic area. A notable exception was among non-Hispanic white women with border residents being more likely to have ever had a mammogram than non-border residents, perhaps due to targeted screening programs in the region.

The U.S. Army Medical Research and Materiel Command under DAMD17-03-1-0274 supported this work.

Syllabus: Genetic Epidemiology

American College of Epidemiology Workshop

June 27, 2005

Toronto, Canada

Molecular Genetics for Epidemiologists: From the basics to the More Advanced

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Outline

- Background on DNA/RNA
  - size, structure, base pairing, types, transcription, translation, gene structure
- Working with DNA
  - general techniques, PCR, sequencing
- Genotyping
  - DNA sources, extraction, handling, polymorphisms, RFLP analysis
- Other techniques
  - site directed mutagenesis, allele specific PCR, chip-based genotyping, Taqman, SSCP, cloning

Grant Abstract: Hormones, Growth Factors and Lipids among Gestational Diabetics and Their Infants

DESCRIPTION: See instructions. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the **mission of the agency**). Describe concisely the research design and methods for achieving these goals. Describe the rationale and techniques you will use to pursue these goals.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to **public** health. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

There is compelling evidence that gestational diabetics with excessive maternal prepregnant adiposity and pregnancy weight gain are themselves and their infants at increased risk of subsequent type 2 diabetes, cardiovascular disease and cancer. Elevated hormones, growth factors and lipids which may lead to these chronic diseases can be controlled by appropriate diet and physical activity. The purpose of this grant is to determine the feasibility of establishing a cohort of gestational diabetics and their infants who will be followed for the length of the project. Specific aims of this grant are 1) to determine the feasibility of establishing a cohort of gestational diabetics and their infants, 2) to determine whether levels of hormones, growth factors and lipids in women with gestational diabetes and their infants differ by maternal prepregnant adiposity and pregnancy weight gain, and 3) to determine the feasibility of developing an intervention to discourage postnatal weight retention in women with gestational diabetes and to encourage normal weight in their children. For the proposed study, primary care clinics in the Lower Rio Grande Valley of Texas will be used to identify a cohort of 300 Mexican American women with a history of gestational diabetes in their immediate past pregnancy who receive prenatal care between January 2007 and December 2008. Subjects who agree to participate will complete a prenatal computer-assisted personal interview covering pregnancy history including complications, maternal weight history, diet and physical activity. Follow-up interviews at birth, one and two years will collect information on pregnancy weight gain, breastfeeding, and maternal and child diet and physical activity. We will collect a fasting blood sample and perform assays of hormones (e.g., insulin, leptin), growth factors (e.g., insulin-like growth factor-I) and lipids (e.g., cholesterol). Blood will also be drawn from the umbilical cord at birth and from the mother one year postpartum. Should the primary care clinics be feasible as a source of subjects based on our indicators of data quality, we will have the needed preliminary data to develop competitive R01s to assess hormones, growth factors and lipids associated with subsequent chronic disease in a larger cohort of gestational diabetics. This prospective cohort study will make a significant contribution of great relevance to NIDDK because it will be used to develop interventions to discourage postnatal weight retention and encourage normal weight in the children of gestational diabetics.

PERFORMANCE SITE(S) (organization, city, state)

The University of Texas Health Science Center at Houston (UTHSCH)
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KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Maureen Sanderson	MSANDERSON	UTHSCH	PI
Gerson Peltz		UTB	Co-PI
Deanna Hoelscher		UTHSCH	Co-I
Nancy Murray		UTHSCH	Co-I

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project

Human Embryonic Stem Cells ☒ **No** ☐ **Yes**

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/registry/index.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

Disclosure Permission Statement. Applicable to SBIR/STTR Only. See SBIR/STTR instructions. ☐ Yes ☐ No

Curriculum vitae

CURRICULUM VITAE

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BACKGROUND:

Education and Training:

1996	**Doctor of Philosophy** Department of Epidemiology, University of Washington
1984	**Master of Public Health** Nutrition and Population Studies Module, University of Texas-Houston School of Public Health
1979	**Bachelor of Science** Department of Human Nutrition, Ohio State University

Honors and Awards:

2003	Texas Department of Health Friends of Public Health Award
1998	Delta Omega Honorary Public Health Society
1997	Sigma Xi Scientific Research Society
1994	Society for Epidemiologic Research Student Workshop
1992-1996	Maternal and Child Health Bureau Traineeship
1983-1984	U.S. Public Health Service Traineeship
1983	Texas Department of Health Fellowship

Professional Experience:

2001-Present	**Associate Professor of Epidemiology** **Investigator, Center for Health Promotion and Prevention Research** University of Texas-Houston School of Public Health, Brownsville Regional Campus
2001-Present	**Associate Professor (Adjunct appointment)** Department of Epidemiology and Biostatistics, University of South Carolina
2000-2005	**Visiting Faculty** Department of Public Health, St. George's University, Grenada
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1991-1994	**Research/Teaching Assistant** Department of Epidemiology, University of Washington
1989-1991	**Survey Statistician** Followback Survey Branch, National Center for Health Statistics
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1987-1989	**Study Manager** Brownsville Infant Feeding Project, University of Texas Medical Branch
1986-1987	**Health Educator/Nutritionist** Hidalgo County Health Care Corporation (DBA Nuestra Clinica del Valle)
1984-1986	**Nutritionist Educator and Acting Program Director** Eastern Caribbean Regional Health Training Facility

RESEARCH EXPERIENCE:

Publications (Peer-reviewed Journals):

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Students are italicized.

Other Publications (Reports/Monographs/Letters/Book reviews):

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2. Doyle DL, **Sanderson M**, Smith U, Fineman RM. Genetic health care in Washington: assessment of services and establishment of a statewide plan. Olympia, WA:Washington State Department of Health, December 1997.

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3. Coker AL, **Sanderson M,** Cantu E, Huerta D, Fadden MK. Frequency and types of partner violence among Mexican American college women. J Am College Health (Submitted March 2006).

4. *Meyer TE*, Coker AL, **Sanderson M**, Symanski E. A case-control study of farming and prostate cancer in African American and Caucasian men. Occup Environ Med (Submitted March 2006).

5. **Sanderson M**, Daling JR, Malone KE, Doody DR. Perinatal factors and mortality from breast cancer. Cancer Epidemiol Biomark Prev (Submitted March 2006).

Invited Speaker:

1. **Sanderson M**, Williams, MA, Daling JR, Holt VL, Self SG, Moore DE. Pregnancy characteristics and breast cancer. National Cancer Institute Workshop on Early Life Exposures and Risk of Breast Cancer, Chantilly, VA, January 1999.

2. Coker AL, **Sanderson M**. Prostate cancer – epidemiological considerations. 152nd Annual Meeting of the South Carolina Medical Association, Charleston, SC, April 2000.

3. **Sanderson M**, Shu XO, Jin F, Dai Q, Yu H, Gao YT, Zheng W. Insulin-like growth factor-I, soyfood intake and breast cancer risk. 3rd Department of Defense Breast Cancer Research Program Meeting, Orlando, FL, September 2002.

4. **Sanderson M.** Dynamics of measuring data for the Hispanic population. DHHS Region VI Title V Maternal and Child Health/Healthy Start Conference, Las Cruces, NM, October 2003.

5. **Sanderson M**, Daling JR, Malone KE, Doody DR, Porter PL. Perinatal factors and mortality from breast cancer. 4th Department of Defense Breast Cancer Research Program Meeting, Philadelphia, PA, June 2005.

6. **Sanderson M.** Fred Hutchinson Cancer Research Center studies of perinatal factors and breast cancer. International Collaborative Group on Prenatal Factors and Breast Cancer, London, England, September 2005.

7. **Sanderson M.** South Texas Women's Health Project. Department of Defense Historically Black Colleges and Universities/Minority Institutions Breast Cancer Research Program Reverse Site Visit, Baltimore, MD, April 2006.

Published Abstracts:

1. **Sanderson M**, Williams MA, Stanford JL, Daling JR. Perinatal factors and risk of breast cancer. Am J Epidemiol 1994;139:S12.

2. **Sanderson M**, Williams MA, Weiss NS. Low dose oral contraceptives and invasive epithelial ovarian cancer. Am J Epidemiol 1995;141:S77.

3. **Sanderson M**, Williams MA, White E, Daling JR, Holt VL, Malone KE, Self SG, Moore DE. Validity and reliability of subject and mother reporting of perinatal factors. Am J Epidemiol 1997;141:S25.

4. **Sanderson M,** Miles L, *Jespersen KM*, Liu Q, Sappenfield WM. An analysis of South Carolina perinatal regionalization using the Medicaid/vital record linked file. Paediatr Perinatal Epidemiol 1998;12:A33.

5. **Sanderson M**, Shu XO, Jin F, Dai Q, Wen WQ, Hui Y, Gao YT, Zheng W. Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study. Am J Epidemiol 2000;151:S63.

6. *Ellison GL*, Coker AL, **Sanderson M**, Hebert JR, Weinrich SP, Lipsitz SR. Psychosocial stress, coping, and prostate cancer. Am J Epidemiol 2000;151:S52.

7. *Callaghan WM*, **Sanderson M**. The association between maternal leisure-time physical activity and the delivery of a macrosomic infant. **Student Prize Paper Award of the Society for Pediatric and Perinatal Epidemiologic Research.** Paediatr Perinatal Epidemiol 2001:15;A6.

8. **Sanderson M**, Shu X-O, Jin F, Dai Q, Ruan Z, Gao Y-T, Zheng W. Weight at birth and adolescence and premenopausal breast cancer in a low-risk population. Am J Epidemiol 2001;153:S36.

9. Coker AL, Davis KE, Desai S, Arias I, Smith PH, **Sanderson M**. Impact of intimate partner violence on men and women: Analysis of the NVAW. Am J Epidemiol 2001;153:S180.

10. Divon M, **Sanderson M**, Minior V, Ferber A, Haglund B, Westgren M. Birth weight for gestational age percentiles in the prediction of perinatal outcome at term. Am J Obstet Gynecol 2001; 184:S57.

11. Divon M, **Sanderson M**, Ferber A, O'Reilly-Green C, Haglund B, Westgren M. Does prolonged pregnancy predict adverse perinatal outcome? Am J Obstet Gynecol 2001; 184:S168.

12. **Sanderson M**, Shu XO, Jin F, Dai Q, Yu H, Gao YT, Zheng W. Adolescent soyfood intake, insulin-like growth factor-I and breast cancer risk. Am J Epidemiol 2002;153:S20.

13. Shields D, Parker D, **Sanderson M**, Magann E, Scardo J, Chauhan S. Detection of fetal growth restriction and discordant growth among twin gestation stratified by placental chorionicity. Am J Obstet Gynecol 2002; 187:S178.

14. Chauhan S, Magann E, Velthius S, Nunn S, **Sanderson M**, Reynolds D, Scardo J, Barrileaux PS, Martin J Jr. Detection of fetal growth restriction in patients with chronic hypertension: the 34 week barrier to accurate sonographic diagnosis. Am J Obstet Gynecol 2002; 187:S178.

15. **Sanderson M**, Coker AL, Logan P, Zheng W, Fadden MK. Lifestyle and prostate cancer among older African-American and Caucasian men in South Carolina. Am J Epidemiol 2004;159:S13.

16. Coker AL, **Sanderson M**, Zheng W, Fadden MK. Diabetes Mellitus and prostate cancer risk among older men: Population-based case-control study. Am J Epidemiol 2004;159:S8.

17. **Sanderson M**, Coker AL, Perez A, Fadden MK. A multilevel analysis of socioeconomic status and prostate cancer risk. Am J Epidemiol 2005;161:S43.

18. Aragaki CC, **Sanderson M**, Coker A, Cai Q, Hayes R, Zheng W. Aryl hydrocarbon receptor SNP *AHR* modifies the effect of pesticide use on prostate cancer in South Carolina. Am J Epidemiol 2005;161:S95.

19. Coker AL, **Sanderson M**, Fadden MK. Psychosocial stress, coping and prostate cancer. Am J Epidemiol 2005;161:S1.

20. Meyer TE, Coker AL, **Sanderson M**, Symanski E. Reduction of exposure misclassification in a case-control study of farming-related exposures and prostate cancer. Am J Epidemiol 2005;161:S1.

Presentations (Exclusive of Published Abstracts):

1. **Sanderson M**, Randall DE. Food consumption patterns of Starr County, Texas WIC participants. Annual Meeting of the Society for Nutrition Education, Philadelphia, PA, June 1984.

2. Simpson G, Lougee-Heimer R, **Sanderson M**. An evaluation of response error on interviews and mailed questionnaires. 117th Annual Meeting of the American Public Health Association, Chicago, IL, October 1989.

3. Wallingford J, **Sanderson M**. Feeding practices in U.S. infants during the first six months. 118th Annual Meeting of the American Public Health Association, New York, NY, October 1990.

4. McLaughlin J, **Sanderson M**. The Special Supplemental Food Program for Women, Infants and Children (WIC): participation during pregnancy and its impact on birth outcome and infant health. 118th Annual Meeting of the American Public Health Association, New York, NY, October 1990.

5. Moss N, **Sanderson M**, Carver K. The effect of medical, social, and behavioral risks upon birth outcome in Hispanic infants. 119th Annual Meeting of the American Public Health Association, Atlanta, GA, October 1991.

6. **Sanderson M**, Wallingford J. Breastfeeding and infantile diarrhea: Results from the 1988 National Maternal and Infant Health Survey. 119th Annual Meeting of the American Public Health Association, Atlanta, GA, October 1991.

7. McLaughlin J, **Sanderson M**. The effects of the WIC program on maternal behavior during pregnancy, birth outcome and infant health. 119th Annual Meeting of the American Public Health Association, Atlanta, GA, October 1991.

8. **Sanderson M**, Emanuel I, Holt VL. Maternal birthweight and infant mortality: Preliminary results from the National Maternal and Infant Health Survey. 120th Annual Meeting of the American Public Health Association, Washington, DC, October 1992.

9. Bentvelzen J, **Sanderson M**, Doyle DL, Fineman RM. Factors which influence the rate of receiving a second newborn screening test in Washington State. Annual Meeting of the National Society of Genetic Counselors, Atlanta, GA, May 1993.

10. Taylor JA, **Sanderson M**. A reexamination of the risk factors for sudden infant death syndrome (SIDS). Annual Meeting of the Association of Ambulatory Pediatrics, Seattle, WA, May 1994.

11. **Sanderson M**, Emanuel I, Holt VL. The intergenerational relationship between mother's birthweight, infant birthweight, and infant mortality in blacks and whites. Annual Meeting of the Teratology Society. Las Croabas, Puerto Rico, June 1994.

12. **Sanderson M**, Doyle DL, Fineman RM. Estimating the prevalence of genetic conditions using capture-recapture methodology. 123rd Annual Meeting of the American Public Health Association, San Diego, CA, October 1995.

13. Randels SP, Clarren SK, **Sanderson M**, Gaudino J, Hymbaugh K, Fineman RM. Population-based fetal alcohol syndrome (FAS) surveillance at elementary school entrance. Annual Meeting of the American Medical Genetics Association, Minneapolis, MN, October 1995.

14. **Sanderson M**, Williams, MA, Daling JR, Holt VL, Self SG, Moore DE. Maternal factors and breast cancer risk among young women. 125th Annual Meeting of the American Public Health Association, Indianapolis, IN, November 1997.

15. *Connelly AE*, **Sanderson M**. Predictors of low birthweight in South Carolina mothers. 126th Annual Meeting of the American Public Health Association, Washington, DC, November 1998.

16. Reininger B, Lindley L, Vincent M, Richter D, Pluto D, Strack R, **Sanderson M**. A theoretical framework for community-based efforts. 126th Annual Meeting of the American Public Health Association, Washington, DC, November 1998.

17. Magann EF, **Sanderson M**, Martin JN, Chauhan SP. The amniotic fluid index, single deepest pocket, and two-diameter pocket in normal human pregnancy. 67th Annual Meeting of the Central Association of Obstetricians and Gynecologists, Maui, HI, October 1999.

18. *Blackhurst D*, Coker AL, *Chesoni M*, **Sanderson M**. Abuse during pregnancy increases risk of term low birth weight. 127th Annual Meeting of the American Public Health Association, Chicago, IL, November 1999.

19. **Sanderson M**, Coker AL, *Blackhurst D*. Abuse during pregnancy increases risk of miscarriage and neonatal death. 127th Annual Meeting of the American Public Health Association, Chicago, IL, November 1999.

20. *Baker R*, **Sanderson M**. Neural tube defects among infants across regions of the United States.127th Annual Meeting of the American Public Health Association, Chicago, IL, November 1999.

21. Reininger B, Burgos M, Vincent M, Royce S, Watkins J, Richter D, Strack R, **Sanderson M,** Pluto D. Collaboration and planning in 13 urban teen pregnancy prevention initiatives: a preliminary report on lessons learned. 127th Annual Meeting of the American Public Health Association, Chicago, IL, November 1999.

22. *Branum AM*, **Sanderson M**, *Harris N*, Coker AL, Chauhan SP. Postpartum pregnancy and the risk of neonatal seizures. 1999 Maternal, Infant, and Child Health Epidemiology Workshop, Atlanta, GA, December 1999.

23. *Helms K*, **Sanderson M**, Coker AL, Addy CL. Predictors of short interpregnancy interval among South Carolina mothers and the association with low birthweight. 1999 Maternal, Infant, and Child Health Epidemiology Workshop, Atlanta, GA, December 1999.

24. *Branum AM*, **Sanderson M**, Petrini J, Addy CL. Impact of multiple births on increasing low birthweight and preterm birth in the US: 1990-1998. 128th Annual Meeting of the American Public Health Association, Boston, MA, November 2000.

25. Chauhan SP, **Sanderson M**, Magann EF. Biometric measurements and regression equations to predict weight: fetal versus neonatal. 45th Annual Meeting of the American Institute of Ultrasound in Medicine, Orlando, FL, March 2001.

26. *Adegoke OJ*, Blair A, Shu XO, **Sanderson M**, Addy CL, Zheng W. Occupational history and exposure and the risk of adult leukemia in Shanghai. 93rd Annual Meeting of the American Association for Cancer Research, San Francisco, CA, April 2002.

27. **Sanderson M**, Fernandez M, Dutton RJ, Ponder A, *Sosa D.* A comparison of risk behaviors among Texas border and non-border residents. 61st Annual Meeting of the US-Mexico Border Health Association, San Diego, CA, May 2003.

28. *Adegoke OJ*, Linet M, Shu XO, **Sanderson M**, Jin F, Addy CL, Zheng W. Smoking, drinking and hair-dye use and the risk of adult leukemia in Shanghai. 94th Annual Meeting of the American Association for Cancer Research, Washington, DC, July 2003.

29. *Shapiro-Mendoza CK*, Selwyn BJ, Smith DP, **Sanderson M**. Joint effects of paternal and maternal pregnancy intention status on early childhood stunting: findings from Bolivia. 131st Annual Meeting of the American Public Health Association, San Francisco, CA, November 2003.

30. Chauhan SP, Hendrix NW, Magann EF, Bofill JA, **Sanderson M**, Morrison JC. Risk factors for neonatal organ damage among newborns at gestational age $\geq$ 34 weeks and umbilical arterial pH $<$ 7.00. 24th Annual Meeting of the Society for Maternal-Fetal Medicine, New Orleans, LA, February 2004.

31. Coker AL, McCurdy S, **Sanderson M**, Eggleston K, Risser JM. Patient knowledge of HPV along the US-Mexico border. 22nd International Papillomavirus Conference and Clinical Workshop, Vancouver, Canada, April 2005

32. Brandt HM, Coker AL, **Sanderson M**, Olson C. Clinician communication of HPV: a qualitative study. 22nd International Papillomavirus Conference and Clinical Workshop, Vancouver, Canada, April 2005

33. *Peltz G*, **Sanderson M**, Perez A, Estrada JK, Johnson M. Use of mammography by Texas-Mexico border residence and ethnicity. 4th Department of Defense Breast Cancer Research Program Meeting, Philadelphia, PA, June 2005.

34. Chauhan SP, Berghella V, **Sanderson M**, Magann EF, Morrison JC. ACOG Practice Bulletins: An overview. 73rd Annual Meeting of the Central Association of Obstetricians and Gynecologists, Scottsdale, AZ, October 2005.

35. *Peltz G*, Casares DO, Fadden MK, *Calil RC*, Perez A, **Sanderson M**. The use of body mass index for the diagnosis of obesity in Mexican Americans: A comparative study with bioelectrical impedance analysis. Annual Meeting of the North American Society on Obesity, Vancouver, CN, October, 2005.

36. *Peltz G*, *Garcia ER*, *Calil RC*, Fadden MK, **Sanderson M**. Self-perception of body image and body area dissatisfaction in Mexican Americans. Annual Meeting of the North American Society on Obesity, Vancouver, CN, October, 2005.

37. **Sanderson M,** Fernandez ME, Dutton RJ, Ponder A, *Sosa D, Peltz G*. Risk behaviors by Texas-Mexico border residence and ethnicity. 133rd Annual Meeting of the American Public Health Association, Philadelphia, PA, November 2005.

38. Chauhan SP, Parker D, Shields D, **Sanderson M**, Cole JH, Scardo JA. Sonographic estimate of birth weight among high-risk patients: factors influencing accuracy. 23rd Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Orlando, FL, January 2006.

39. Perez A, Reininger BM, Aguirre Flores MI, **Sanderson M**, Roberts RE. Physical activity and overweight among adolescents on the Texas-Mexico border. 5th Annual Hawaii International Conference on Statistics, Mathematics and Related Field, Honolulu, HI, January 2006.

Grant and Contract Awards:

Current:

2005-2006 Principal Investigator (0% concurrent support): Partnership between the Texas Cancer Registry and the UTSPH-B for Assuring Timely, Complete and Accurate Cancer Data in the Lower Rio Grande Valley of Texas. Supported by a grant from the Texas Cancer Council ($146,011 total direct) to improve cancer registration and cancer data on the Texas-Mexico border, and to build capacity for a qualified cancer registration workforce.

2004-2006 Co-Investigator (U48/DP000057-01, 3% support): Trial of Interventions to Increase Utilization of Colorectal Cancer Screening and Promote Informed Decision Making About Colorectal Cancer Screening Among Hispanic Men and Women. Supported by a cooperative agreement from the Centers for Disease Control and Prevention ($258,436 total direct) to develop interventions for colorectal cancer screening along the Texas-Mexico Border. (Principal Investigator: Maria Fernandez)

2004-2006 Consultant (2% support): Serum Leptin Values in Mexican Americans: Association with Body Fat, Body Mass Index, and Obesity. Supported by a grant to the University of Texas at Brownsville from the U.S. Hispanic Nutrition Research and Education Center ($49,856 total direct) to investigate the association between serum leptin and measures of body fat (Principal Investigator: Gerson Peltz)

2004-2007 Mentor for Gerson Peltz (0% concurrent support): Minority Biomedical Research Support Research Initiative for Scientific Enhancement. Supported by grant to the University of Texas at Brownsville from the National Institute of General Medical Sciences ($1,495,440 total direct) to enhance and expand research and research training in biomedical sciences. (Principal Investigator: Eldon Nelson)

2003-2008 Principal Investigator, Cancer Core and Training Core (MD000170 P20, 15-26% support): Creation of an Hispanic Health Research Center in the Lower Rio Grande Valley. Supported by a grant from the National Center on Minority Health and Health Disparities ($4,948,500 total direct) to create a Hispanic Health Research Center in the Lower Rio Grande Valley of Texas. (Principal Investigator: Joseph McCormick)

2003-2007 Principal Investigator, Subcontract (DAMD17-03-1-0274, 0-10% concurrent support): Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women. Supported by a grant from the Department of Defense ($179,694 total direct) to train faculty from the University of Texas at Brownsville to conduct breast cancer research. (Principal Investigator, University of Texas at Brownsville: Gerson Peltz)

2000-2006 Principal Investigator (DAMD17-00-1-0340, 50% support): Interrelationships of Prenatal and Postnatal Growth, Hormones, Diet and Breast Cancer. Supported by a grant from the Department of Defense ($158,900 total direct) to conduct research with senior investigators on breast cancer as it relates to nutritional, genetic and molecular epidemiology.

Pending:

2006-2007 Principal Investigator (20%support): Using the Texas Cancer Registry to Conduct a Multiethnic Prostate Cancer Study. The proposed study would be supported by a grant from the national Cancer Institute ($274,997 total direct) to determine the feasibility of using data from the Texas Cancer Registry as a source of cases for subsequent population-based case-control studies.

Previous:

2002-2004 Co-Investigator (U48/CCU609653-SIP-02-02, 3% support): Cancer Prevention and Control Network. Supported by a cooperative agreement from the Centers for Disease Control and Prevention ($707,100 total direct) to establish a Cancer Prevention and Control Network for Texas and surrounding states along the Texas-Mexico Border. (Principal Investigator: Maria Fernandez)

2002-2004 Co-Investigator (7% support): Lower Rio Grande Valley Nutrition Intervention Research Initiative. Supported by a contract from the United States Department of Agriculture ($195,000 total direct) to produce a monograph on the nutrition services and research in the Lower Rio Grande Valley of Texas. (Principal Investigator: R. Sue Day)

2002-2003 Principal Investigator (02IPA24671, 10% support): Brownsville-Matamoros Sister City Project. Supported by a contract from the Centers for Disease Control and Prevention ($45,479 total direct) to establish a system of women's health surveillance on the US-Mexico border.

2000-2003 Principal Investigator (S1135-19/20, 25% support): Multilevel Analysis of Socioeconomic Status and Prostate Cancer Risk. Supported by a cooperative agreement from the Association of Schools of Public Health/Centers for Disease Control and

Prevention ($207,000 total direct) to investigate the association between socioeconomic status, stress, coping, and prostate cancer.

2000-2001 Principal Investigator (0% support): Buccal Cell Collection for the South Carolina Older Men's Health Project. Supported by a contract from the National Cancer Institute ($16,400 total direct) to assess the role of some genetic factors in the development of prostate cancer.

1998-2001 Principal Investigator (5% support): Program to Prevent and Reduce Medicaid Utilization. Supported by a contract from the South Carolina Department of Health and Human Services ($593,600 total direct) to develop and maintain the Alzheimer's Disease Registry.

1998-2001 Co-Investigator (5% support): Evaluation Plan of the South Carolina Adolescent Pregnancy Prevention Initiative. Supported by a grant from the South Carolina Department of Social Services ($725,000 total direct) to evaluate county-specific efforts to reduce adolescent pregnancy. (Principal Investigator: Murray Vincent)

1997-1999 Principal Investigator (0% support): Breast Cancer Risk Factors among Older Women in the Midlands, South Carolina. Supported by a grant from the University of South Carolina, Research and Productive Scholarship Award ($9,500 total direct) to assess the feasibility of using the statewide cancer registry to conduct a case-control study of breast cancer.

1997-1999 Principal Investigator (0% support): Using the South Carolina Central Cancer Registry to Conduct a Case-Control Study of Prostate Cancer. Supported by a grant from the South Carolina Cancer Center ($20,000 total direct) to assess the feasibility of using the statewide cancer registry to conduct a case-control study of prostate cancer.

1997-1998 Co-Investigator (5% support): Preventing Teen Pregnancy: Sharing Lessons Learned. Supported by a cooperative agreement from the Centers for Disease Control and Prevention ($137,000 total direct) to evaluate CDC-funded teen pregnancy prevention projects. (Principal Investigator: Murray Vincent)

1997-1998 Principal Investigator (10% support): Pregnancy Risk Assessment Monitoring System. Supported by a contract from the South Carolina Department of Health and Environmental Control ($23,593 total direct) to supervise Pregnancy Risk Assessment Monitoring System analyses.

SERVICE:

Professional Service:

2005-present Member, Editorial Board, Paediatric and Perinatal Epidemiology
2005 Member, Special Emphasis Review Panel, Centers for Disease Control and Prevention
2005 Member, Reproductive Health Grant Review Panel, Centers for Disease Control and Prevention
2004-present Member, Human Subjects Research and Review Committee, University of Texas at Brownsville

2002-present	Member, International Collaborative Group on Prenatal Factors in Breast Cancer
1999-present	Abstract Reviewer, Epidemiology Section, American Public Health Association
2004	Member, Institutional Research Training Grant Review Panel, Centers for Disease Control and Prevention
2004	Member, Clinical and Experimental Therapeutics Peer Review Panel, Prostate Cancer Review Program, Department of Defense
2002-2003	Member, US-Mexico Border Chronic Disease Initiative, Centers for Disease Control and Prevention
2000-2001	Member, Grant Review Committee, South Carolina Cancer Center
2000	Member, Special Emphasis Review Panel, Centers for Disease Control and Prevention
1999-2001	Abstract Reviewer, Maternal and Child Health Section, American Public Health Association
1999	Co-chair, Epidemiology Section Program Planning Committee, American Public Health Association

Journal Reviewer:

American Journal of Epidemiology
American Journal of Obstetrics and Gynecology
American Journal of Public Health
Ambulatory Child Health
Annals of Epidemiology
BMC Public Health
BMC Womens' Health
Cancer Causes and Control
Cancer Epidemiology Biomarkers and Prevention
Ehtnicity and Disease
Family and Community Health
International Journal of Cancer
JAMA
Journal of Adolescence
Journal of Clinical Epidemiology
Journal of the National Cancer Institute
Journal of Reproductive Medicine
Journal of Women's Health and Gender-Based Medicine
Maternal and Child Health Journal
Paediatric and Perinatal Epidemiology

Institutional Service:

2005	Member, Peer Review Committee, University of Texas-Houston School of Public Health
2005-present	Chair-elect, Faculty, University of Texas-Houston School of Public Health
2004-present	Member, Committee for the Protection of Human Subjects, University of Texas Health Science Center at Houston
2004-present	Member, New Investigator Development Program Steering Team, University of Texas Health Science Center at Houston
2004-present	Member, Epidemiology Division Leadership Team, University of Texas-Houston School of Public Health

2003-present	Member, Epidemiology Division Search Committee, University of Texas-Houston School of Public Health
2004-2005	Member, Practice Council, University of Texas-Houston School of Public Health
2003	Member, Nominations Committee for Epidemiology Division Director, University of Texas-Houston School of Public Health
2002-2003	Chair, Student Research Funds Review Committee, University of Texas-Houston School of Public Health
2002-2003	Member, Curriculum Committee, Epidemiology Discipline, University of Texas-Houston School of Public Health
2001-2003	Member, Admissions Committee, Brownsville Regional Campus, University of Texas-Houston School of Public Health
2001	Member, Peer Review Committee, University of Texas-Houston School of Public Health
2000-2001	Member, Continuing and Distance Education Committee, School of Public Health, University of South Carolina
1998-2001	Faculty Affiliate, Women's Studies Program, University of South Carolina
1998-2000	Member, Comprehensive Exam Committee, Department of Epidemiology and Biostatistics, School of Public Health, University of South Carolina
1997-2000	Member, Faculty Senate, University of South Carolina
1996-2000	Member, Health Ethics Committee, School of Public Health, University of South Carolina
1996-2001	Member and Chair, Curriculum Committee, Department of Epidemiology and Biostatistics, School of Public Health, University of South Carolina
1996-1998	Member, Admissions Committee, Department of Epidemiology and Biostatistics, School of Public Health, University of South Carolina

Public Health Practice Service:

2003-present	Co-chair, Texas Cancer Data Work Group Data Utilization Subcommittee, Texas Department of State Health Services
2002-present	Board Member and President, Planned Parenthood of Cameron and Willacy Counties
2001-present	Member, Lower Rio Grande Valley Nutrition Intervention Research Initiative
2001-present	Member, Healthy Communities of Brownsville, Inc.
2002-2003	Consultant, Office of Border Health, Texas Department of Health
2002-2003	Member, Health Data Analysis and Monitoring Work Group, Willacy County
2001-2003	Consultant, Community Oriented Primary Care (COPRIMA), Brownsville
2000-2001	Member, Infant Mortality Work Group, South Carolina Department of Health and Environmental Control
1999-2001	Member, Data Committee for Improving Pregnancy Outcomes, South Carolina Department of Health and Environmental Control
1997-2001	Member, Universal Newborn Hearing Screening Council, South Carolina Department of Health and Environmental Control
1997-1999	Member, Community Health Assessment Work Group, South Carolina Department of Health and Environmental Control
1997-1998	Member, Maternal and Child Health Work Group, South Carolina Department of Health and Environmental Control
1996-1999	Member, Public Health Task Force, South Carolina Cancer Center

Active Member:

2002-present	US-Mexico Border Health Association
1999-present	American Association for Cancer Research
1996-2001	South Carolina Cancer Center
1992-present	Society for Epidemiologic Research
1992-present	Society for Pediatric and Perinatal Epidemiologic Research
1981-present	American Public Health Association

TEACHING:

Classes Taught:

Course	Dates	Role	Number of Students	Student Evaluations
University of Texas-Houston School of Public Health, Brownsville Regional Campus				7 is exceptional
Introduction to Epidemiology	Fall 2001	Instructor	13	6.87
	Fall 2002	Instructor	20	6.58
	Fall 2003	Instructor	10	6.13
	Fall 2004	Instructor	5	
	Fall 2005	Instructor	34	
Introduction to Public Health Research Computing	Spring 2002	Instructor	1	7
	Summer 2003	Instructor	4	6.25
Statistical Methods in Epidemiologic Research	Fall 2002	Co-Instructor (33%)	2	7
Advanced Epidemiologic Methods I	Spring 2003	Co-Instructor (33%)	24	6.28
	Spring 2004	Co-Instructor (33%)	12	6.67
	Fall 2004	Co-instructor (33%)	46	
	Fall 2005	Co-instructor (33%)	43	
Nutritional Epidemiology	Spring 2004	Co-Instructor (50%)	11	6.93
Cancer Epidemiology	Summer 2005	Co-instructor (50%)	19	
University of South Carolina				5 is exceptional
Introduction to Epidemiology	Fall 1996	Co-Instructor (75%)	65	3.91
Epidemiologic Methods I	Spring 1997	Instructor	27	3.71
	Spring 1998	Instructor	37	2.90
	Spring 1999	Co-Instructor (50%)	25	3.35
Epidemiologic Methods II	Fall 1997	Co-Instructor (75%)	19	2.75
Epidemiology Doctoral Seminar	Fall 1997	Instructor	12	3.08
	Fall 1998	Instructor	7	4.17
Women's Health	Fall 1999	Co-Instructor (50%)	12	3.27
Epidemiologic Concepts in Selected Diseases or Health Conditions	Spring 2000	Instructor	12	4.64
	Spring 2001	Instructor	13	4.77
Effective Data Management for Public Health	Fall 2000	Instructor	26	4.00

Thesis/Dissertation Supervisor:

Student	Completed	Title
University of Texas-Houston School of Public Health, Brownsville Regional Campus		
Passion Sparrow	2003	Cancer screening behaviors and perceptions of health among Hispanic women
Gerson Peltz	2006	Serum leptin concentration, adiposity, and body fat distribution in Mexican Americans: A cross-sectional study
University of South Carolina		
Jing Wang	1998	Comorbidity associated with dementia
Lexi Connelly	1998	Maternal stress as an explanatory factor for the black-white birthweight disparity in South Carolina women
Greg Kirkner	1999	Implementing an electronic lab data reporting system at South Carolina's Central Cancer Registry: feasibility and practicality considerations
Joyce Yu	1999	A descriptive study of fetal death in South Carolina, 1990-1995
Julie Hudson	1999	Body mass index and prostate specific antigen concentration among African American men
Kristen Helms	1999	Predictors of short interpregnancy interval among South Carolina mothers and its association with low birthweight
Bill Callaghan	2000	The association between maternal leisure-time physical activity and the delivery of a macrosomic infant
Michael Idowu	2000	Utilizing pathology reports for predicting prostate Cancer Stage
Amy Branum	2000	Impact of multiple births on increasing low birthweight and preterm birth in the US: 1990-1998
Puja Verma	2000	Amniocentesis and preterm delivery in twin pregnancies
John Benjamin	2001	Prevalence of dementia in South Carolina: application of capture-recapture methodology
Beili Dong	2001	Partner violence during pregnancy and risk of adverse pregnancy outcomes
Ginie Daguise (PhD)	2001	Childhood leukemia: the role of maternal pregnancy conditions and childhood infections, and reliability of maternal reporting